Petition
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,378,703

EXPRESS MAILING LABEL NO. EH623959242US

Issued: January 3, 1995

Assignee: Alcon Laboratories, Inc.

9200 6-11-98

Attention: BOX PATENT EXTENSION

TRANSMITTAL OF FEE UNDER 37 C.F.R. §1.20(j)

Honorable Commissioner of Patents
and Trademarks
BOX PATENT EXTENSION
Washington, D. C. 20231

Dear Sir:

An application for extension of the term of the above-identified patent has been filed herewith. Please charge the $1,120.00 fee required under 37. C.F.R. §§1.740(a)(14) and 1.20(j) to Deposit Account No. 01-0682. The Commissioner is hereby authorized to charge any additional fees which may be required. A duplicate of this paper is attached.

Respectfully submitted,
ALCON LABORATORIES, INC.

Date: May 28, 1998

By: _____
Sally Yeager
Registration No. Reg. 32,757

Address for Correspondence:
Sally Yeager - (O-148)
Patent Department
Alcon Laboratories, Inc.
6201 So. Freeway
Fort Worth, TX 76134-2099
(817) 551-4031

Attorney Docket No.: 11158C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,378,703

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Dear Sir:

An application for extension of the term of the above-identified patent has been filed herewith. Please charge the $1,120.00 fee required under 37. C.F.R. §§1.740(a)(14) and 1.20(j) to Deposit Account No. 01-0682. The Commissioner is hereby authorized to charge any additional fees which may be required. A duplicate of this paper is attached.

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ALCON LABORATORIES, INC.

Date: May 28, 1998

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Sally Yeager - (Q-148)
Patent Department
Alcon Laboratories, Inc.
6201 So. Freeway
Fort Worth, TX 76134-2099
(817) 551-4031

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,378,703

Express Mailing Label No. EH623959242US

Issued: January 3, 1995

Assignee: Alcon Laboratories, Inc.

Attention: BOX PATENT EXTENSION

APPLICATION FOR EXTENSION OF TERM UNDER 35 U.S.C. §156

Honorable Commissioner of Patents
and Trademarks
BOX PATENT EXTENSION
Washington, D.C. 20231

Dear Sir:

Alcon Laboratories, Inc. ("Alcon") hereby applies for extension of the term of United States Patent No. 5,378,703.

BACKGROUND

Alcon is the owner of United States Patent No. 5,378,703 (sometimes referred to herein as the '703 patent). Photocopies of the Assignment and Notice of Recordation are attached as Appendix A.

The '703 patent is directed to novel compounds, formulations comprising the compounds, and methods for controlling intraocular pressure with the compounds. The first compound of Claim 7 is known as brinzolamide. Brinzolamide is also covered in the compound Claims 1-6.

Brinzolamide is the active ingredient of a new ophthalmic pharmaceutical product developed by Alcon. That product is known as AZOPT™ (brinzolamide ophthalmic suspension) 1%. The United States Food and Drug Administration (FDA) granted Alcon's application for approval to market this product on April 1, 1998. The product is referred to hereinafter as "the approved product."

As explained below, it is believed that the '703 patent is eligible for an extension of term under the provision of 35 U.S.C. §156. Alcon has therefore submitted this Application for Extension of Term in accordance with 35 U.S.C. §156 and the applicable Patent Office regulations (i.e., 37 C.F.R. §§ 1.710, et. seq.).

ELIGIBILITY

United States Patent No. 5,378,703 is eligible for extension under the provisions of 35 U.S.C. §156(a) and 37 C.F.R. §§1.710 and 1.720. The criteria for eligibility are set forth below:

(1) the '703 patent claims, among other things, a method for using the approved product to treat elevated intraocular pressure;

(2) the term of the '703 patent has not expired prior to submission of this Application;

(3) the term of the '703 patent has never been previously extended;

(4) no other patent has been extended based on the regulatory review period for the approved product;

(5) the approved product has been subject to a regulatory review period of the type defined in 35 U.S.C. §156(g)(1)(A);

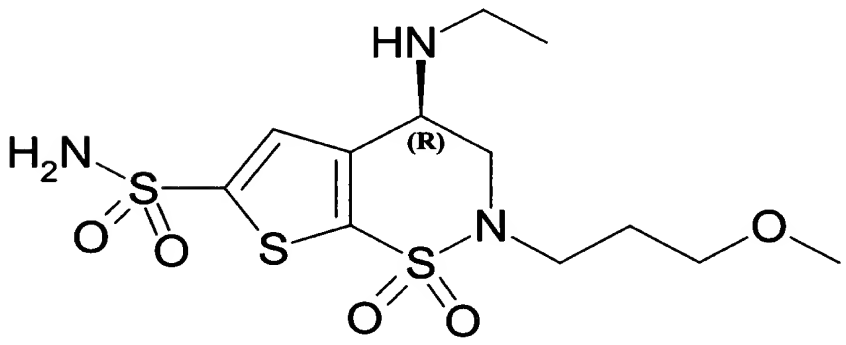
(6) the permission for commercial marketing or use of the approved product resulting from the regulatory review period is the first permitted commercial marketing or use of any human drug product containing the active ingredient contained in the approved product (i.e., brinzolamide); and

(7) an application for extension of term meeting the requirements of 35 U.S.C. §156(d) has been submitted within the period specified in 35 U.S.C. §156(d)(1).

APPLICATION

In accordance with the requirements of 35 U.S.C. §156(d) and 37 C.F.R. §§ 1.730 and 1.740, Alcon presents the following information. The paragraph numbers utilized below correspond to the paragraph numbers under subparagraph (a) of 37 C.F.R. §1.740:

(1) The approved product is a sterile ophthalmic suspension which contains brinzolamide (1%) as its sole active ingredient. Brinzolamide has the following structural formula:



Further details concerning this compound are presented in the USP Dictionary of USAN and International Drug Names; a copy of page 106 of that publication is attached as Appendix B. Further details concerning the approved product are presented in the FDA-approved package insert; a copy of that insert is attached as Appendix C.

(2) The regulatory review occurred under Sections 505(i) and 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et. seq.)

(3) The approved product received FDA approval under Section 505(b) of the Federal Food, Drug, and Cosmetic Act on April 1, 1998. A copy of the approval letter is attached as Appendix D.

(4) As stated above, the active ingredient of the approved product is

brinzolamide. This compound has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This Application is being submitted within the sixty (60) day period specified in 35 U.S.C. §156(d)(1) and 37 C.F.R. §1.720(f), which period expires on May 30, 1998.

(6) The patent for which an extension is being sought is United States Patent No. 5,378,703. This patent was issued to Thomas R. Dean, Hwang-Hsing Chen, and Jesse A. May on August 31, 1993, and will expire on April 9, 2010.

(7) A copy of United States Patent No. 5,378,703 in the form of a cut-up copy wherein only a single column is reproduced on each page is attached as Appendix E.

(8) Two Terminal Disclaimers and a Certificate of Correction have been filed in connection with United States Patent No. 5,378,703 and copies of all are a part of Appendix E. (During prosecution of this case the Examiner requested Terminal Disclaimers relative to two prior cases, i.e., U.S. Patent Nos. 5,153,192 and 5,240,923. Two Disclaimers were filed, but inadvertently they were both directed to the '192 patent which expires on April 9, 2010. However, the face of the '703 patent sought to be extended here reflects the Disclaimer that was to be filed relative to the '923 patent which expires on August 31, 2010). A new Terminal Disclaimer to accurately disclaim any portion beyond August 31,

2010, of the '923 patent has been filed as evidenced in Appendix E. The first maintenance fee was paid on May 5, 1998, but a statement has not yet been received. A copy of the Maintenance Fee Transmittal Form and Return Card is attached as Appendix F.

(9) United States Patent No. 5,378,703 claims brinzolamide, formulations for controlling intraocular pressure comprising brinzolamide, and a method for controlling intraocular pressure with brinzolamide. Brinzolamide is the active ingredient of the approved product. As indicated in the package insert (see Appendix C, page 3), the approved product is indicated for treatment of elevated intraocular pressure in patients with ocular hypertension or open angle glaucoma.

The use of the approved product to treat intraocular pressure is specifically set forth in Claim 14 of the '703 patent. Claim 14 reads as follows:

> 14. A method for controlling intraocular pressure which comprises topically administering to the affected eye a therapeutically effective amount of the compound of Claim 7.

[Note: Claim 7 referred to in Claim 14 is directed to several compounds, including brinzolamide (the first compound of the claim.)

Relevant Dates and Information pursuant to 35 U.S.C. §156(g)

(11) The relevant dates and information specified in 35 U.S.C. §156(g) are as follows:

(a) IND 40,152

The investigational new drug ("IND") application was filed on July 24, 1992. The IND application was assigned serial number 40,152.

(b) NDA 20-816

The new drug application ("NDA") was submitted on January 28, 1997. The NDA was assigned serial number 20-816. The NDA was approved on April 1, 1998.

Brief Description of Activities During the Regulatory Review Period

The activities undertaken by Alcon during the regulatory review periods identified in paragraph (1) above were as follows:

(a) 7/24/92 - 7/23/93

Investigational new Drug application No. 40,152 (hereinafter "IND") was submitted to the FDA under Section 505(i) of the Federal Food, Drug and Cosmetic Act on July 24, 1992. A Phase I clinical safety study and a Phase I Ocular Comfort Study were then initiated with the first applications of the approved product taking place on August 25, 1992. In addition with this safety study and additional clinical studies, informational and protocol amendments were submitted to the FDA in August, September, October, and November of 1992 and January, February, April, and June of 1993. Teleconferences with the FDA Medical Reviewers concerning the design of clinical studies occurred in September of 1992 and a dose-reponse study was initiated in glaucoma patients. In addition, toxicology studies were conducted to permit longer-term evaluations of the drug in clinical studies.

(b) 7/24/93 - 7/23/94

Annual progress Report No. 1 was submitted to the FDA. Informational and protocol amendments were submitted to the FDA in September, November, and December, of 1993 and January, March, June, and July, of 1994. Teleconferences with the FDA Medical reviewers concerning clinical study design occurred in September 1993 and June of 1994. Requests for an

End-of-Phase II meeting were made in March and April of 1994. The briefing packet was submitted in May 1994 and the Meeting occurred on May 24, 1994. Alcon's minutes to this meeting were submitted in June of 1994 and FDA's minutes were requested in July of 1994. Clinical studies were initiated to evaluate adjunctive therapy in glaucoma patients and to evaluate the effect of formulation changes on efficacy and duration of action. A study was done to compare efficacy in BID and TID dosing. Studies were also conducted to qualify a new commercial supplier for the drug substance.

(c) 7/24/94 - 7/23/95

Annual Progress Report No. 2 was submitted to the FDA. Informational and protocol amendments were submitted to the FDA in September of 1994 and June and July of 1995. Teleconferences were held with the FDA medical reviewers in July of 1995. A request for a second End-of-Phase II meeting was made in February, the briefing packet was submitted in April and the Meeting occurred in May of 1995. Alcon's minutes to this meeting were submitted in July of 1995. During this period the BID/TID dose regimen study was completed and a QID study was initiated and completed. Draft protocols for the Phase III program were provided to the FDA Medical Reviewers for comment and long-term toxicology studies were completed to support the longer-term clinical exposure to occur in Phase III.

(d) 7/24/95 - 7/23/96

Annual Progress Report No. 3 was submitted to the FDA. Informational and protocol amendments were submitted to

the FDA in September, October, November, and December of 1995 and January February, March, April, June, and July of 1996. Teleconferences were held with the FDA medical reviewers in December of 1995 and June of 1996. A request for a carcinogenicity waiver was submitted in February 1996. The Phase III clinical program was initiated including studies to confirm safety and efficacy as both a primary and adjunctive therapy in reducing intraocular pressure. A long-term topical study was also initiated to evaluate long-term safety and efficacy and affects on corneal health. Changes were also made to improve the manufacturability of the drug product and the planned commercial site was added to the IND as a source for clinical supplies. A special orally dosed clinical study was initiated to evaluate steady state pharmacokinetics and level of carbonic anhydrase inhibition. Two special studies designed to comparatively evaluate ocular comfort with repeated dosing in glaucoma studies were also initiated.

(e) 7/24/96 - 7/23/97

Annual Progress Report No. 4 was submitted to the FDA. Informational and protocol amendments were submitted to the FDA in August, September, and November of 1996 and February of 1997. In August, a Pre-NDA meeting was requested in order to review the content and format of the NDA with the FDA. A briefing packet was provided in October and the Meeting was held in October with minutes of the meeting submitted in December of 1996. New Drug Application No. 20-816 (hereinafter "NDA") was submitted to the FDA on January 28, 1997. Amendments to the NDA and responses to FDA

reviewers' requests were submitted in February, March, May, and June of 1997. During this period, the Phase III clinical program was completed to support the NDA submission. The long-term safety study was extended to be an 18-month study based upon FDA input received at the pre-NDA meeting and an oral pharmacokinetic/carbonic anhydrase study was initiated in renally impaired subjects. A special clinical study to examine the effects of the drug on ocular blood flow was also initiated and studies were initiated and completed to qualify an additional commercial supplier for the manufacture of the drug substance.

(f) 7/24/97 - Present

Amendments to the NDA were made in November and December of 1997 and January, February, March, and April of 1998. The NDA was approved on April 1, 1998.

(g) Summary

The testing phase, beginning in August of 1992, was characterized by continuous and uninterrupted clinical safety and efficacy studies through the time of NDA filing on January 28, 1997. Subsequent to the NDA filing, Alcon continuously and diligently sought approval of its NDA covering the approved product. There were no periods between July 24, 1992, and April 1, 1998, during which Alcon did not actively pursue approval from the FDA for commercial marketing of the approved product.

Statement of Applicant's Opinion Concerning Eligibility for an Extension and the Length of the Extension

(12) In the opinion of Alcon, United States Patent No. 5,378,703 is eligible for an extension of 579 days. The length of the extension was calculated as follows:

(a) IND Period

The IND period began on July 24, 1992, and ended on January 27, 1997. The IND period therefore included a total of 1,648 days. The '703 patent issued on January 3, 1995, 893 days after the IND period began. Therefore the IND period for calculation purposes is 755 days (i.e., 1,648 days minus 893 days). One-half of this total is 377 days.

(b) NDA Period

The NDA period began on January 28, 1997, and ended on April 1, 1998. The NDA period therefore included a total of 428 days.

(c) Length of Extension

The regulatory review period for purposes of patent term extension was 805 days (i.e., 377 days plus 428 days).

(d) Limitation on Extension

Under the provision of 35 U.S.C. §156(c)(3), the term of a patent remaining after the date of product approval cannot exceed fourteen years. In the present case, this means that the term of the '703 patent cannot be extended beyond April 1, 2012. Therefore, it is the opinion of Applicant that only 579 days of the 805 regulatory review period days available for patent extension may be utilized.

(13) Alcon hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension requested herein.

(14) The accompanying Transmittal Letter requests that the $1,120.00 fee required by 37 C.F.R. §1.20(j) be charged to Deposit Account No. 01-0682.

(15) Alcon requests that all correspondence and inquiries in connection with this Application be directed to the following individual:

Sally S. Yeager
Patent Department, Q-148
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
Phone: (817) 551-4031
Fax: (817) 551-4610

(16) A certified duplicate of this Application is being filed herewith.

(17) A Declaration meeting the requirements of 37 C.F.R. §1.740(b) is attached.

Based on the foregoing, it is believed that United States Patent No. 5,378,703 is entitled to an extension of 579 days. An official notice to that effect in the form of a certificate of extension is respectfully requested.

Respectfully submitted,

ALCON LABORATORIES, INC.

Date May 28/1998

By _____
Sally Yeager
Registration No. 32,757

Address for Correspondence:
Sally Yeager
Patent Department, Q-148
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
Phone: (817) 551-4031

Docket No. 1158C

DECLARATION

This Application is submitted pursuant to extension of the term of United States Patent No. 5,378,703. The undersigned, as agent for Alcon Laboratories, Inc. ("Alcon"), the owner of said patent, hereby declares:

THAT I am an attorney of record in connection with United States Patent No. 5,378,703 and am authorized to act on behalf of Alcon in patent matters;

THAT I have reviewed and understand the contents of the attached Application papers consisting of a fourteen page Application, a Declaration, and Appendices A-F;

THAT I believe United States Patent No. 5,378,703 is subject to extension pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.710;

THAT I believe an extension of 579 days is fully justified under 35 U.S.C. §156 and the applicable regulations;

That I believe United States Patent No. 5,378,703 meets the conditions for extension of the term of a patent, as set forth in 37 C.F.R. §1.720; and

THAT all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this Application and any extension of United States Patent No. 5,378,703.

ALCON LABORATORIES, INC.

Date May 28, 1998

By _____
Sally Yeager
Registration No. 32,757

#15
attachment

APPENDIX A

Assignment and Recordation Sheet

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DATE: 03/21/94
TO:

N05A

SALLY YEAGER
ALCON LABORATORIES, INC.
PATENT DEPT., MC Q-148
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT ASSIGNMENT PROCESSING SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT BRANCH, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231

ASSIGNOR: DOC DATE: 02/21/94
DEAN, THOMAS ROBERT

ASSIGNOR: DOC DATE: 02/21/94
CHEN, HWANG HSING

ASSIGNOR: DOC DATE: 02/21/94
MAY, JESSE ALBERT

RECORDATION DATE: 02/28/94 NUMBER OF PAGES 004 REEL/FRAME 6879/0076

DIGEST : ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE:
ALCON LABORATORIES, INC.
PATENT DEPARTMENT, MC Q-148
6201 SOUTH FREEWAY
FORT WORTH, TX 76131-2099

SERIAL NUMBER 8-019011 FILING DATE 02/18/93
PATENT NUMBER ISSUE DATE 00/00/00

EXAMINER/PARALEGAL
ASSIGNMENT BRANCH
ASSIGNMENT/CERTIFICATION SERVICES DIVISION

APR 12 1994

FORM PTO-1595
1-31-92

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof

1. Name of conveying party(ies):
Thomas Robert Dean;
Hwang Hsing Chen;
Jesse Albert May

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Address of receiving party(ies):

Name: Alcon Laboratories, Inc.

Internal Address: Patent Department, MC Q-148

Street Address: 6201 South Freeway

City: Fort Worth State: TX ZIP: 76134-2099

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other

Execution Date: February 21, 1994

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
08/019,011

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Sally Yeager

Internal Address: Patent Dept., MC Q-148
ALCON LABORATORIES, INC.

Street Address: 6201 South Freeway

City: Fort Worth State: TX ZIP: 76134-2099

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40.00
☐ Enclosed
☒ Authorized to be charged to deposit account

8. Deposit account number:
01-0682

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Sally Yeager
Name of Person Signing

Signature

Feb 23, 1994
Date

Total number of pages including cover sheet: four (4)

CMB No. 0651-0011 (exp. 4/94)

Do not detach this portion

Mail documents to be recorded with required cover sheet information to:

Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

Public burden reporting for this sample cover sheet is estimated to average about 30 minutes per document to be recorded, including time for reviewing the document and gathering the data needed, and completing and reviewing the sample cover sheet. Send comments regarding this burden estimate to the U.S. Patent and Trademark Office, Office of Information Systems, PK2-1000C, Washington, D.C. 20231, and to the Office of Management and Budget, Paperwork Reduction Project (0651-0011), Washington, D.C. 20503.

US14272 03/07/94 08019011 01-0682 140 581 40.00CH

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ASSIGNMENT BRANCH

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ASSIGNMENT

WHEREAS I am a below named inventor of the invention entitled:

SULFONAMIDES USEFUL AS CARBONIC ANHYDRASE INHIBITORS

and described in a United States Patent Application Serial No. 08/019,011 filed with the United States Patent and Trademark Office on February 18, 1993, and further identified by Attorney Docket No. 1158C.

WHEREAS, ALCON LABORATORIES, INC., a company organized under the laws of Delaware and having a place of business at 6201 South Freeway, Fort Worth, Texas, 76134, is desirous of acquiring the entire right, title and interest in and to said invention and to any and all Letters Patent of the United States and foreign countries which may be obtained therefor;

NOW, THEREFORE, for good and valuable consideration, I do hereby sell, assign and transfer to ALCON LABORATORIES, INC., its legal representatives, successors, and assigns, the entire right, title and interest in and to said invention as set forth in the above-mentioned application, and in and to any and all patents of the United States and foreign countries which may be issued for said invention;

UPON SAID CONSIDERATIONS, I hereby agree that I will not execute any writing or do any act whatsoever conflicting with these presents, and that I will, at any time upon request, without further or additional consideration but at the expense of said assignee, execute such additional assignments and other writings and do such additional acts as said assignee may deem necessary or desirable to perfect the assignee's enjoyment of this grant and render all necessary assistance in making application for and obtaining original, divisional, reexamined, reissued, or other Letters Patent of the United States or of any and all foreign countries on said invention and in enforcing any rights in action accruing as a result of such

applications or patents, said assistance to include my cooperation in all prosecution associated with obtaining such applications or patents and my provision of testimony in any proceedings or transactions involving such applications or patents, it being understood that the foregoing covenant and agreement shall bind, and inure to the benefit of, the assigns and legal representatives of assignor and assignee.

AND I request the Commissioner of Patents and Trademarks to issue any Letters Patent of the United States which may be issued for said invention to said ALCON LABORATORIES, INC., its legal representatives, successors or assigns, as the sole owner of the entire right, title and interest in said patent and the invention covered thereby.

Full name of inventor: Thomas Robert Dean

Inventor's signature: Thomas Robert Dean

Date: 2/21/94

Residence and Post Office Address: 101 Meadow View Court, Weatherford, Texas 76087

Citizenship: United States of America

STATE OF TEXAS §
§
COUNTY OF TARRANT §

On this 21st day of February, 1994, before me personally appeared Thomas Robert Dean, to me known to be the person named in and who executed the above instrument, and acknowledged to me he/she executed the same for the uses and purposes therein set forth.

PHYLISS A. EWING
NOTARY PUBLIC
State of Texas
Comm. Exp. 10-03-96

Phyliss A. Ewing
Notary Public

Full name of inventor: Hwang-Hsing Chen

Inventor's signature: Hwang-Hsing Chen

Date: 2/21/94

Residence and Post Office Address: 3100 Clovermeadow Drive
Fort Worth, Texas 76123

Citizenship: United States of America

STATE OF TEXAS §
§
COUNTY OF TARRANT §

On this 21st day of February, 1994, before me personally appeared Hwang-Hsing Cheng, to me known to be the person named in and who executed the above instrument, and acknowledged to me he/she executed the same for the uses and purposes therein set forth.

PHYLISS A. EWING
NOTARY PUBLIC
State of Texas
Comm. Exp. 10-03-96

Phyliss A. Ewing
Notary Public

Full name of inventor: Jesse Albert May

Inventor's signature: Jesse Albert May

Date: 2-21-94

Residence and Post Office Address: 4108 Longmeadow Way
Fort Worth, Texas 76133

Citizenship: United States of America

STATE OF TEXAS §
§
COUNTY OF TARRANT §

On this 21st day of February, 1994, before me personally appeared Jesse Albert May, to me known to be the person named in and who executed the above instrument, and acknowledged to me he/she executed the same for the uses and purposes therein set forth.

PHYLISS A. EWING
NOTARY PUBLIC
State of Texas
Comm. Exp. 10-03-96

Phyliss A. Ewing
Notary Public

APPENDIX B

A copy of page 106 from USP Dictionary of USAN and International Drug Names

USP Dictionary

of USAN and International Drug Names

98

"Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in the *USAN and the USP Dictionary of Drug Names*." [21 CFR 299.4]

A compilation of the United States Adopted Names (USAN) selected and released from June 15, 1961, through January 31, 1997, current USP and NF names for drugs, and other nonproprietary drug names, the *USP Dictionary* incorporates the text previously published under the title *USAN and the USP Dictionary of Drug Names*.

Executive Vice President/Jerome A. Halperin

Editor/Joan Ross Canada, Ph.D.
Coordinator, USP Dictionary of USAN and International Drug Names Program

Research Associate/Maria C. Robie, Ph.D.

Research Assistant/AnnaMarie J. Sibik

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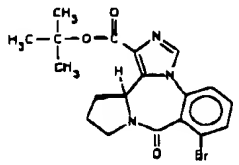
U.S. Pharmacopeia
12601 Twinbrook Parkway, Rockville, MD 20852

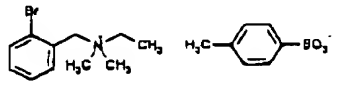
carboxylic acid, 8-bromo-11,12,13,13a-tetrahydro-9-oxo-, 1,1-dimethylethyl ester, (*S*)-; (2) *tert*-Butyl (*S*)-8-bromo-11,12,13,13a-tetrahydro-9-oxo-9*H*-imidazo[1,5-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-1-carboxylate. *CAS-84379-13-5.* INN. *Anti-anxiety agent.* (Hoffmann-LaRoche†) ✧*Ro 16-6028/000*



Brethaire. Ciba-Geigy brand of Terbutaline Sulfate.

Brethine. Ciba-Geigy brand of Terbutaline Sulfate.

Bretylium Tosylate *[1976]* (bre til' ee um). **USP.** $C_{18}H_{24}BrNO_3S$. 414.37. [Bretylium Tosilate is INN.] (1) Benzenemethanaminium, 2-bromo-*N*-ethyl-*N*,*N*-dimethyl-, salt with 4-methylbenzenesulfonic acid (1:1); (2) (*o*-Bromobenzyl)ethyldimethylammonium *p*-toluenesulfonate. *CAS-61-75-6; CAS-59-41-6* [bretylium]. BAN. *Anti-adrenergic; cardiac depressant (anti-arrhythmic).* (Astra); (Elkins-Sinn) ✧*ASL-603*



Brevicon. Syntex brand of combination product; *See* Ethinyl Estradiol; Norethindrone.

Brevital Sodium. Lilly brand of Methohexital Sodium.

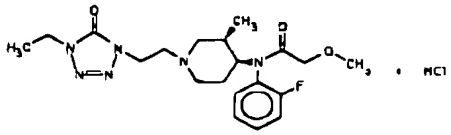
Brevoxyl. Stiefel brand of Benzoyl Peroxide.

Brexin EX. Savage† brand of combination product; *See* Guaifenesin; Pseudoephedrine Hydrochloride.

Brexin L.A. Savage brand of combination product; *See* Chlorpheniramine Maleate; Pseudoephedrine Hydrochloride.

Bricanyl. Merrell brand of Terbutaline Sulfate.

Brifentanil Hydrochloride *[1990]* (bri fen' ta nil). $C_{20}H_{29}FN_6O_3.HCl$. 456.95. [Brifentanil is INN.] (1) Acetamide, *N*-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl)-ethyl]-3-methyl-4-piperidinyl]-*N*-(2-fluorophenyl)-2-methoxy-, monohydrochloride, *cis*-(±)-; (2) (±)-*cis*-*N*-[1-[2-(4-Ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-3-methyl-4-piperidyl]-2'-fluoro-2-methoxyacetanilide monohydrochloride. *CAS-117268-95-8; CAS-101345-71-5* [brifentanil]. *Analgesic (narcotic).* (Anaquest) ✧*A-3331*

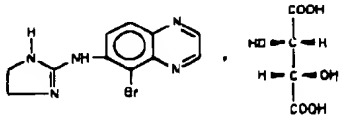


Brij 30. ICI Americas brand of Laureth 4.

Brij 96. ICI Americas† brand of Polyoxyl 10 Oleyl Ether.

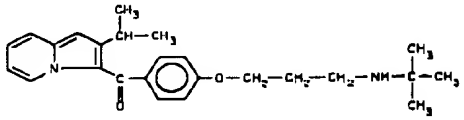
Brij 97. ICI Americas brand of Polyoxyl 10 Oleyl Ether.

Brimonidine Tartrate *[1991]* (bri moe' ni deen). $C_{11}H_{10}BrN_5.C_4H_6O_6$. 442.23. [Brimonidine is INN.] (1) 6-Quinoxalinamine, 5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-, [*S*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1); (2) 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline D-tartrate (1:1). *CAS-79570-19-7; CAS-59803-98-4* [brimonidine]. *Adrenergic (ophthalmic).* Alphagan (Allergan) ✧*UK-14304-18; AGN 190342-LF*

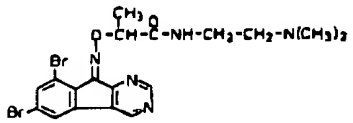


Brinase (INN) — *See* Brinolase.

Brinazarone. $C_{35}H_{32}N_2O_4$. 392.54. *p*-[3-(*tert*-Butylamino)propoxy]phenyl 2-isopropyl-3-indolizinyl ketone. *CAS-89622-90-2.* INN.

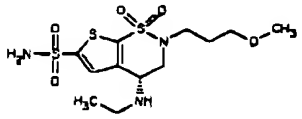


Brindoxime. $C_{18}H_{19}Br_2N_5O_2$. 497.19. 2-[[(6,8-Dibromo-9*H*-indeno[2,1-*d*]pyrimidin-9-ylidene)amino]oxy]-*N*-[2-(dimethylamino)ethyl]propionamide. *CAS-55837-17-7.* INN.

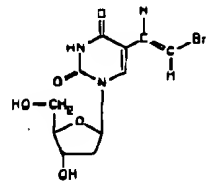


Brinolase *[1971]* (brye' noe lase). [Brinase is INN.] Fibrinolytic enzyme produced by *Aspergillus oryzae.* (1) Proteinase, Aspergillus oryzae, fibrinolytic; (2) Fibrinolytic enzyme of *Aspergillus oryzae. CAS-42615-60-1. Fibrinolytic.* (Connaught, Canada) ✧*CA-7; Protease 1*

Brinzolamide *[1997]* (brin zoh' la mide). $C_{12}H_{21}N_3O_5S_3$. 383.52. (1) 2*H*-Thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide, 4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-, 1,1-dioxide, (*R*)-; (2) (*R*)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide. *CAS-138890-62-7.* INN. *Antiglaucoma agent.* (Alcon) ✧*AL-4862*



Brivudine. $C_{11}H_{13}BrN_2O_5$. 333.14. (*E*)-5-(2-Bromovinyl)-2'-deoxyuridine. *CAS-69304-47-8.* INN.



BRL-284. Code designation for Levopropylcillin Potassium.

BRL-804. Code designation for Hetacillin.

BRL-1241. Code designation for Methicillin Sodium.

BRL-1288. Code designation for Benapryzine Hydrochloride.

BRL-1341. Code designation for Ampicillin.

BRL-1621. Code designation for Cloxacillin Sodium.

BRL-1702. Code designation for Dicloxacillin.

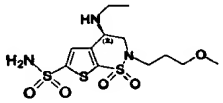
APPENDIX C

A copy of the FDA-approved package insert for the approved product

Azopt (brinzolamide ophthalmic suspension) 1%

DESCRIPTION

AZOPT™ (brinzolamide ophthalmic suspension) 1% contains a carbonic anhydrase inhibitor formulated for multidose topical ophthalmic use. Brinzolamide is described chemically as: (R)-(+)-4-Ethylamino-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno [3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide. Its empirical formula is $C_{12}H_{21}N_3O_5S_3$, and its structural formula is:



Brinzolamide has a molecular weight of 383.5 and a melting point of about 131°C. It is a white powder, which is insoluble in water, very soluble in methanol and soluble in ethanol.

AZOPT 1% is supplied as a sterile, aqueous suspension of brinzolamide which has been formulated to be readily suspended and slow settling, following shaking. It has a pH of approximately 7.5 and an osmolality of 300 mOsm/kg. Each mL of AZOPT 1% contains 10 mg brinzolamide. Inactive ingredients are mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. Benzalkonium chloride 0.01 % is added as a preservative.

DM-00

CLINICAL PHARMACOLOGY

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBCs), but also in other tissues. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

AZOPT 1 % contains brinzolamide, an inhibitor of carbonic anhydrase II (CA-II). Following topical ocular administration, brinzolamide inhibits aqueous humor formation and reduces elevated intraocular pressure. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its affinity for CA-II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life in whole blood (approximately 111 days). In humans, the metabolite N-desethyl brinzolamide is formed, which also binds to CA and accumulates in RBCs. This metabolite binds mainly to CA-I in the presence of brinzolamide. In plasma, both parent brinzolamide and N-desethyl brinzolamide concentrations are low and generally below assay quantitation limits (<10 ng/mL). Binding to plasma proteins is approximately 60%. Brinzolamide is eliminated predominantly in the urine as unchanged drug. N-Desethyl brinzolamide is also found in the urine along with lower concentrations of the N-desmethoxypropyl and O-desmethyl metabolites.

An oral pharmacokinetic study was conducted in which healthy volunteers received 1 mg capsules of brinzolamide twice per day for up to 32 weeks. This regimen approximates the amount of drug delivered by topical ocular administration of AZOPT (brinzolamide ophthalmic suspension) 1% dosed to both eyes three times per day and simulates systemic drug and metabolite concentrations similar to those achieved with long-term topical dosing. RBC CA activity was measured to assess the degree of systemic CA inhibition. Brinzolamide saturation of RBC CA-II was achieved within 4 weeks (RBC concentrations of approximately 20 µM). N-Desethyl brinzolamide accumulated in RBCs to steady-state within 20-28 weeks reaching concentrations ranging from 6-30 µM. The inhibition of CA-II activity at steady-state was approximately 70-75%, which is below the degree of inhibition expected to have a pharmacological effect on renal function or respiration in healthy subjects.

In two, three-month clinical studies, AZOPT (brinzolamide ophthalmic suspension) 1% dosed three times per day (TID) in patients with elevated intraocular pressure (IOP), produced significant reductions in IOPs (4 -5 mmHg). These IOP reductions are equivalent to the reductions observed with TRUSOPT® (dorzolamide hydrochloride ophthalmic solution) 2% dosed TID in the same studies.

In two clinical studies in patients with elevated intraocular pressure, AZOPT 1% was associated with less stinging and burning upon instillation than TRUSOPT® 2%.

INDICATIONS AND USAGE

AZOPT™ Ophthalmic Suspension 1% is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

AZOPT™ is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

AZOPT™ is a sulfonamide and although administered topically it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of AZOPT. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

PRECAUTIONS

General:

Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. The effect of continued administration of AZOPT on the corneal endothelium has not been fully evaluated.

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. AZOPT has not been studied in patients with acute angle-closure glaucoma.

AZOPT has not been studied in patients with severe renal impairment (CrCl < 30 mL/min). Because AZOPT and its metabolite are excreted predominantly by the kidney, AZOPT is not recommended in such patients.

AZOPT has not been studied in patients with hepatic impairment and should be used with caution in such patients.

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and AZOPT. The concomitant administration of AZOPT and oral carbonic anhydrase inhibitors is not recommended.

Information For Patients:

AZOPT™ is a sulfonamide and although administered topically, it is absorbed systemically; therefore, the same types of adverse reactions attributable to sulfonamides may occur with topical administration. Patients should be advised that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician (see **WARNINGS**).

Vision may be temporarily blurred following dosing with AZOPT. Care should be exercised in operating machinery or driving a motor vehicle.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures or other surfaces, since the product can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.
The preservative in AZOPT™ Ophthalmic Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of AZOPT, but may be reinserted 15 minutes after instillation.

Drug Interactions:
AZOPT™ Ophthalmic Suspension 1% contains a carbonic anhydrase inhibitor. Acid-base and electrolyte alterations were not reported in the clinical trials with brinzolamide. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of drug interactions have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interaction should be considered in patients receiving AZOPT.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenicity data on brinzolamide are not available. The following tests for mutagenic potential were negative: (1) *in vivo* mouse micronucleus assay; (2) *in vivo* sister chromatid exchange assay; and (3) Ames *E. coli* test. The *in vitro* mouse lymphoma forward mutation assay was negative in the absence of activation, but positive in the presence of microsomal activation.
In reproduction studies of brinzolamide in rats, there were no adverse effects on the fertility or reproductive capacity of males or females at doses up to 18 mg/kg/day (375 times the recommended human ophthalmic dose).

Pregnancy:
Teratogenic Effects: Pregnancy Category C. Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 62, and 125 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (375 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.
There are no adequate and well-controlled studies in pregnant women. AZOPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:
In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (312 times the recommended human ophthalmic dose) were seen during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma.
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from AZOPT, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

Adverse Reactions:
In clinical studies of AZOPT (brinzolamide ophthalmic suspension) 1%, the most frequently reported adverse events associated with AZOPT 1% were blurred vision and bitter, sour or unusual taste. These events occurred in approximately 5-10% of patients. Blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis were reported at an incidence of 1-5%.
The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

OVERDOSAGE
Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following oral administration of an overdose. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

DOSAGE AND ADMINISTRATION
Shake well before use. The recommended dose is 1 drop of AZOPT Ophthalmic Suspension in the affected eye(s) three times daily.
AZOPT may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure.
If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

HOW SUPPLIED
AZOPT™ Ophthalmic Suspension 1% is supplied in plastic DROP-TAINER® dispensers with a controlled dispensing-tip as follows:

NDC 0065-0275-24	2.5 mL
NDC 0065-0275-05	5 mL
NDC 0065-0275-10	10 mL
NDC 0065-0275-15	15 mL

Storage: Store AZOPT Ophthalmic Suspension 1% at 4-30°C (39-86°F).

℞ Only

U.S. Patent Numbers: 5,240,923; 5,378,703; 5,461,081; patents pending.

*TRUSOPT is a registered trademark of Merck & Co., Inc.

April 1998

236026-0498

Alcon®
OPHTHALMIC
Alcon Laboratories, Inc.
Fort Worth, Texas 76134 USA

APPENDIX D

FDA Approval Letter of April 1, 1998

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-816

APR 1 1998

Desk Copy

Alcon Laboratories, Inc.
Attention: D. Scott Krueger
Director, Regulatory Affairs
P.O. Box 6600
Fort Worth, Texas 76115

Dear Mr. Krueger:

Please refer to your new drug application dated January 26, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AZOPT™ (brinzolamide ophthalmic suspension), 1%. We also refer to the approvable letter dated December 4, 1997.

We acknowledge receipt of your submissions dated November 26, and December 11 and 15, 1997, and January 27 and 28, February 4, March 9, and April 1, 1998.

This new drug application provides for Azopt for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated April 1, 1998. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical in content to the April 1, 1998, draft labeling. Marketing the product with FPL that is not identical may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-816. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Lori Gorski, Project Manager, at (301) 827-2090.

Sincerely,

MWeintraub 4/1/98

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPENDIX E

A cut-up copy of United States Patent No. 5,378,703

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,378,703

DATED : January 3, 1995

INVENTOR(S) : Dean, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 46, line 3, change ". . . (=0)R_7 or R_5 . . ." to ". . . (=O)R_7 or R_5 . . ."

Column 47, line 24, insert [3,2-e] between "thieno" and "1".

Column 47, line 27, insert [3,2-e] between "thieno" and "-".

Column 47, line 30, insert [3,2-e] between "thieno" and "-".

Column 47, line 32, insert [3,2-e] between "thieno" and "-".

Column 47, line 34, insert [3,2-e] between "thieno" and "-".

Column 47, line 37, insert [3,2-e] between "thieno" and "-".

Column 47, line 40, insert [3,2-e] between "thieno" and "-".

Column 47, line 43, insert [3,2-e] between "thieno" and "-".

Column 47, line 46, insert [3,2-e] between "thieno" and "-".

Column 47, line 49, insert [3,2-e] between "thieno" and "-".

Column 47, line 52, insert [3,2-e] between "thieno" and "-".

Column 47, line 55, insert [3,2-e] between "thieno" and "-".

Column 47, line 58, insert [3,2-e] between "thieno" and "-".

Column 47, line 61, insert [3,2-e] between "thieno" and "-".

Column 48, line 2, insert [3,2-e] between "thieno" and "-".

Column 48, line 5, insert [3,2-e] between "thieno" and "-".

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,378,703

DATED : January 3, 1995

INVENTOR(S) : Dean, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 48, line 8, insert [3,2-e] between "thieno" and "-".

Column 48, line 11, insert [3,2-e] between "thieno" and "-".

Column 48, line 14, insert [3,2-e] between "thieno" and "-".

Column 48, line 17, insert [3,2-e] between "thieno" and "-".

Column 48, line 20, insert [3,2-e] between "thieno" and "-".

Column 48, line 23, insert [3,2-e] between "thieno" and "-".

Column 48, line 26, insert [3,2-e] between "thieno" and "-".

Column 48, line 29, insert [3,2-e] between "thieno" and "-".

Column 48, line 32, insert [3,2-e] between "thieno" and "-".

Column 48, line 35, insert [3,2-e] between "thieno" and "-".

Column 48, line 37, insert [3,2-e] between "thieno" and "-".

Column 48, line 40, insert [3,2-e] between "thieno" and "-".

Signed and Sealed this

Twenty-ninth Day of April, 1997

Attest:

Attesting Officer

BRUCE LEHMAN

Commissioner of Patents and Trademarks

US005378703A

United States Patent [19]

Dean et al.

[11] Patent Number: 5,378,703

[45] Date of Patent: * Jan. 3, 1995

[54] **SULFONAMIDES USEFUL AS CARBONIC ANHYDRASE INHIBITORS**

[75] Inventors: **Thomas R. Dean**, Weatherford; **Hwang-Hsing Chen; Jesse A. May**, both of Fort Worth, all of Tex.

[73] Assignee: **Alcon Laboratories, Inc.**, Fort Worth, Tex.

[*] Notice: The portion of the term of this patent subsequent to Aug. 31, 2010 has been disclaimed.

[21] Appl. No.: **19,011**

[22] Filed: **Feb. 18, 1993**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 775,313, Oct. 9, 1991, Pat. No. 5,240,923, which is a continuation-in-part of Ser. No. 618,765, Nov. 27, 1990, Pat. No. 5,153,192, which is a continuation-in-part of Ser. No. 506,780, Apr. 9, 1990, abandoned.

[51] **Int. Cl.**[6] **C07D 513/04**; A61K 31/54

[52] **U.S. Cl.** **514/222.8**; 544/48

[58] **Field of Search** 544/48; 514/222.8

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,619,939	10/1986	Maren	514/363
4,731,368	3/1988	Hoffman, Jr. et al.	514/301
4,746,745	5/1988	Maren	548/139

US005378703A

United States Patent [19]

Dean et al.

[11] Patent Number: 5,378,703

[45] Date of Patent: * Jan. 3, 1995

4,797,413 1/1989 Baldwin et al. 514/432
4,847,289 7/1989 Baldwin et al. 514/445

FOREIGN PATENT DOCUMENTS

661731 4/1963 Canada .
1516024 6/1978 United Kingdom .

OTHER PUBLICATIONS

"The Reactions of Some Thiophene Sulfonyl Derivatives," Cremyln et al., *Phosphorus and Sulfur*, vol. 10, pp. 111–119, 1981.

"Studien in der Thiophenreihe. XXIV.[2] Uber Nitrothiophene and Thiophensulfochloride," Steinkopf et al., *Justus Liebigs Analen Der Chemie*, vol. 501, pp. 174–186, 1933.

"Heterocyclic Disulphonamides and Their Diuretic Properties," deStevens et al., *Journal of Medicinal and Pharmaceutical Chemistry*, vol. 1(6), pp. 565–576, 1959.

Gronowitz et al., *Thiophene and its Derivatives*, vol. 44, Pt. 3, pp. 135–307 (1986).

Primary Examiner—John M. Ford
Attorney, Agent, or Firm—Sally Yeager

[57] ABSTRACT

Sulfonamides and pharmaceutical compositions containing the compounds useful in controlling intraocular pressure are disclosed. Methods for controlling intraocular pressure through administration of the compositions are also disclosed.

14 Claims, No Drawings

SULFONAMIDES USEFUL AS CARBONIC ANHYDRASE INHIBITORS

This application is a continuation-in-part of U.S. Pat. application Ser. No. 07/775,313, filed Oct. 9, 1991, now U.S. Pat. No. 5,240,903, which is a continuation-in-part of U.S. Pat. application Ser. No. 618,765, filed Nov. 27, 1990, now U.S. Pat. No. 5,153,192, which is a continuation-in-part of U.S. Pat. application Ser. No. 506,780, filed Apr. 9, 1990, now abandoned.

Field of the Invention

The present invention relates to new sulfonamides useful in lowering and controlling intraocular pressure.

BACKGROUND OF THE INVENTION

Glaucoma is a disease of the eye which is characterized by a progressive loss of visual field due to irreversible damage to the optic nerve to the point where if untreated can result in total blindness. This loss of visual field, in one form of primary open angle glaucoma, or POAG, is associated with a sustained increase in the intraocular pressure (IOP) of the diseased eye. Moreover, elevated intraocular pressure without visual field loss is thought to be indicative of the early stages of this form of POAG.

There are a number of therapies that target reducing the elevated IOP associated with this form of POAG. The most common feature the topical administration of a beta adrenergic antagonist or a muscarinic agonist. These treatments while effective in lowering IOP can also produce significant undesirable side effects.

Another less common treatment for this form of POAG is the systemic administration of carbonic anhydrase inhibitors. However, these drugs also can bring about unwanted side effects, such as nausea, dyspepsia, fatigue, and metabolic acidosis.

U.S. Pat. Nos. 4,797,413, 4,847,289 and 4,731,368 disclose topically dosed thiophene sulfonamides which lower IOP by inhibiting carbonic anhydrase.

Thiophene bis-sulfonamides, which are carbonic anhydrase inhibitors useful for treating conditions attributable to a restriction of blood flow to the brain, including atherosclerosis, occlusion of blood vessels in the brain, stroke and other cerebra vascular diseases, are disclosed in the British Patent No. 1,516,024. Similar compounds are also disclosed in *Justus Liebigs Annalen der Chemie*, 1933, 501, 174–188 and in Phosphorus Sulfur, 1981, 10(1), 111–119.

Other thiophene bis-sulfonamides, which are carbonic anhydrase inhibitors useful as diuretics, are disclosed in the German Patent No. 1,096,916 and *Journal of Medicinal and Pharmaceutical Chemistry*, 1959, 1(6), 565–576.

The compounds of the present invention are new sulfonamides which are carbonic anhydrase inhibitors useful for lowering IOP without producing significant systemic side effects when delivered topically to the eye.

SUMMARY OF THE INVENTION

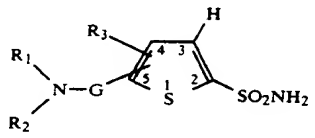
The present invention is directed to new sulfonamides which can be used to lower and control IOP. The compounds are formulated in pharmaceutical compositions for delivery.

The invention is also directed to methods for lowering and controlling IOP by the administration of the

compositions comprising the sulfonamides of the present invention. The compositions can be administered systemically and/or topically to the eye.

DETAILED DESCRIPTION OF THE INVENTION

The sulfonamides of the present invention have the following structure.



I

or a pharmaceutically acceptable salt thereof wherein:

R_1 is H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$.

R_2 is H; C_{1-8} alkyl; C_{2-8} alkyl substituted with OH, NR_5R_6, halogen, C_{1-4} alkoxy, C_{2-4}alkoxyC_{1-4}alkoxy, $OC(=O)R_7$, or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-3} alkyl substituted with phenyl or R_{10} either of which can be unsubstituted or substituted optionally with C_1-C_3alkyl, C_1-C_3halo alkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2; C_{2-4} alkoxy substituted optionally with NR_5R_6, halogen, C_{1-4} alkoxy, or $C(=O)R_7$; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with C_1-C_3alkyl, C_1-C_3halo alkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2; provided that R_1 and R_2 cannot both be H; or R_1 and R_2 can be joined to form a saturated ring of 5 or 6 atoms selected from O, S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine, thiazolidine 1,1 dioxide, or tetrahydrooxazine, which can be unsubstituted or substituted optionally on carbon with OH, NR_5R_6, halogen, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl, C_{1-6} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on nitrogen with NR_5R_6, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$.

R_3 is H; halogen; C_{1-4} alkyl; C_{1-8} alkoxy; C_{1-8} alkylthiol; C_{2-8} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkyl substituted optionally with R_4; or R_1 and R_3 can be joined together with carbon atoms to form a ring of from 5 to 7 members in which said carbon atoms can be unsubstituted or substituted optionally with R_4.

R_4 is OH; C_{1-4} alkyl unsubstituted or substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; NR_5R_6; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2;

Provided that when G is SO_2 and R_3 is in the 4 position and is H or halogen then R_1 and R_2 are not H, C_{1-6} alkyl substituted optionally with OH, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkenyl, phenyl, phenoxy, pyridyl, tetrahydrofuryl, C_{2-6} alkanoyl, C_{2-6} alkenyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms selected optionally from C, O, S, N in which said nitrogen, when saturated, is substituted optionally with H or C alkyl or in which said carbon is substituted optionally with C alkyl, C_{1-6} alkoxy or OH; and when R_3 is in the 5 position and is H, Cl , Br, or C_{1-3} alkyl then neither R_1 nor R_2 can be H or C_{1-4} alkyl; and when G is C(=O) and in the 5- position and R_3 is H, then R_1 and R_2 cannot both be CH_3;

R_5 & R_6 are the same or different and are H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or C(=O)R_7; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, halogen, C_{1-4} alkoxy or C(=O)R_7; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-2}alkylC_{35}cycloalkyl; C(=O)R_7 or R_5 and R_6 can be joined to form a ring of 5 or 6 atoms selected from O , S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine or thiazolidine 1,1-dioxide, which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C_{1-4} alkoxy, C(=O)R_7, C_{6-1} alkyl, C_{1-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, C(=O)R_7 or on nitrogen with C_{1-4} alkoxy, C(:O)R_7, S(=O)$_m$$R_8$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, C(:O)R_7 or on sulfur by (=O)$_m$, wherein m is 0–2.

R_7 is C_{1-8} alkyl; C_{1-8} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or C(=O)R_9; C_{1-4} alkoxy; alkoxy substituted optionally with OH, NR_5R_6, halogen or C_{1-4} alkoxy; NR_5R_6; or phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, halogen, C_{1-3} alkyl, C_{1-3} haloalkoxy, $(CH_2)_nNR_5R_6$, S(=O)$_m$$R_8$ or $SO_2NR_5R_6$, wherein n is 0 or 1 and m is 0–2.

R_8 is C_{2-4} alkyl; C_{2-4} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or C(=O)R_7.

R_9 C_{1-4} alkoxy; amino, C_{1-3} alkylamino, or di-C_{1-3} alkylamino; and

R_{10} is a monocyclic ring system of 5 or 6 atoms composed of C, N, O, and/or S, such as furan, thiophene, pyrrole, pyrazole, imidazole, triazole, tetrazole, oxazole, isoxazole, isothiazole, thiazole, thiadiazole, pyridine, pyrimidine, pyridazine, and pyrazine.

G is C(=O) or SO_2.

In the above definitions, the total number of carbon atoms in a substituent group is indicated by the C_{i-j} prefix where i and j are numbers from 1 to 8 for example. This C_{i-j} definition includes both the straight and branched chain isomers. For example, C_{1-4} alkyl would designate methyl through the butyl isomers; and C_{1-4} alkoxy would designate methoxy through the butoxy isomers.

The term "halogen," either alone or in compound words such as "haloalkyl, " means fluorine, chlorine, bromine or iodine Further, when used in compound words such as "haloalkyl," said alkyl may be partially

or fully substituted with halogen atoms, which may be the same or different.

Structure I includes isomers, wherein R_3 and GNR_1R_2 are attached to the 4 and 5 position respectively or R_3 is attached to the 5 position and GNR_1R_2 is attached to the 4 position. Many of the novel compounds of Structure I possess one or more chiral centers and this invention includes all enantiomers, diastereomers and mixtures thereof.

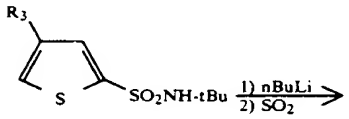
In addition to the following teaching, U.S. Pat. Nos. 5,153,192 and U.S. Pat. No. 5,240,923, the parents of this case which are commonly assigned, are incorporated herein by reference, particularly for their synthesis teaching and their many specific examples.

Compounds of the present invention can be prepared using a variety of procedures, a number of which are described below.

Many of the novel compounds of Structure I can be prepared from 5-sulfamoyl-thiophene-2-sulfonyl chlorides or 3-substituted 5-sulfamoyl-thiophene-2-sulfonyl chlorides, or where it is particularly advantageous for subsequent reactions in a specific preparation that the sulfonamide group be protected, 3-substituted 5-(N-t-butylsulfamoyl)-thiophene-2-sulfonyl chlorides can be used. These thiophene-2-sulfonyl chlorides can be readily prepared by a variety of procedures known in the art, for example see Gronowitz et al in *Thiophene and its Derivatives*, Vol. 44, Pt. 3, p135. The preparative sequence for novel compounds of Structure I using a protected sulfonamide is illustrated in Equation 1. In general, N-t-butyl-thiophene-2-sulfonamides can be selectively metallated at C5 using a strong organometallic base such as n-butyllithium, subsequent condensation with sulfur dioxide gas produces the intermediate lithium sulfinate salts (Equation 1a). The intermediate sulfinate salt can be readily converted to the corresponding sulfonyl chloride with an appropriate chlorinating agent such as N-chlorosuccinimide; amination of the sulfonyl chloride with a primary alkylamine, primary arylamine, or secondary alkylamine, bearing the desired R_1 and R_2 substituents, provides, following deprotection, the novel compounds of Structure I (Equation 1b).

In many cases it is more advantageous initially to prepare simplified primary or secondary sulfonamides as described above, but then append the more complex R_1 or R_2 substituents using standard alkylation reactions (Equation 1c). This sequence can furnish directly certain novel compounds of Structure I; however, subsequent modification of the substituents R_1, R_2, and R_3 can furnish yet other novel compounds of Structure I including novel fused bicyclic compounds; all of which can be prepared using methods known to one skilled in the art. Primary sulfonamides can be prepared from the corresponding sulfonyl chlorides by amination with ammonia or directly from the lithium sulfinate salts using hydroxylamine-O-sulfonic acid (HOSA) (Equation 1d). Equation 1

a)



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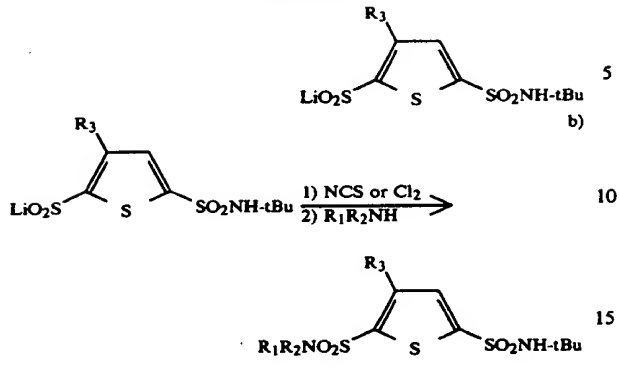
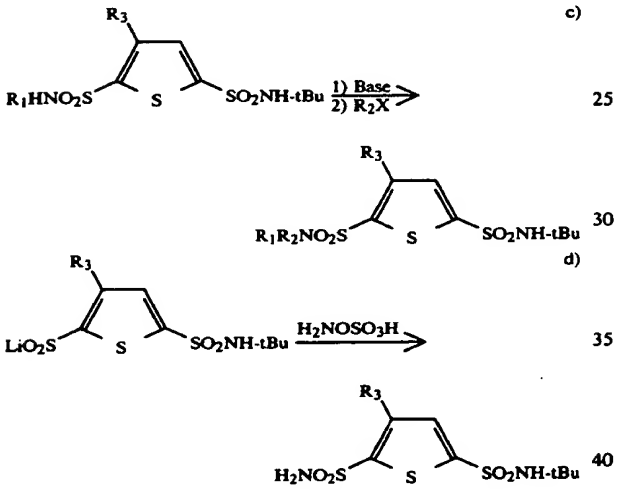
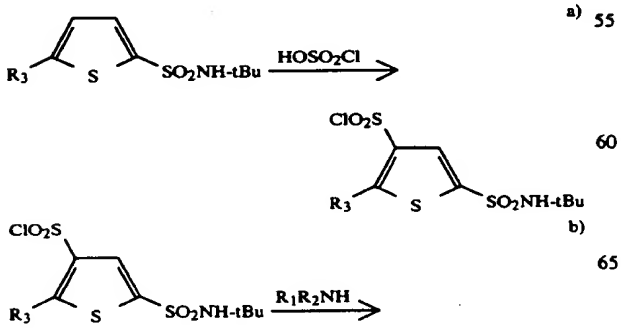


Equation 1 (continued)



Many of the compounds of Structure I can be prepared using the procedures shown below in Equation 2 or other methods known in the art. Chlorosulfonation of thiophene-2-sulfonamides produces the 4-sulfonyl chlorides (Equation 2a). These intermediate sulfonyl chlorides can be converted to the novel compounds of Structure I using procedures (Equations 2b and 2c) analogous to those described for Equation 1.

Equation 2



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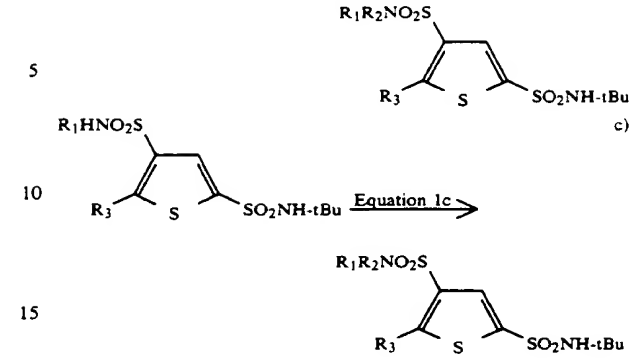
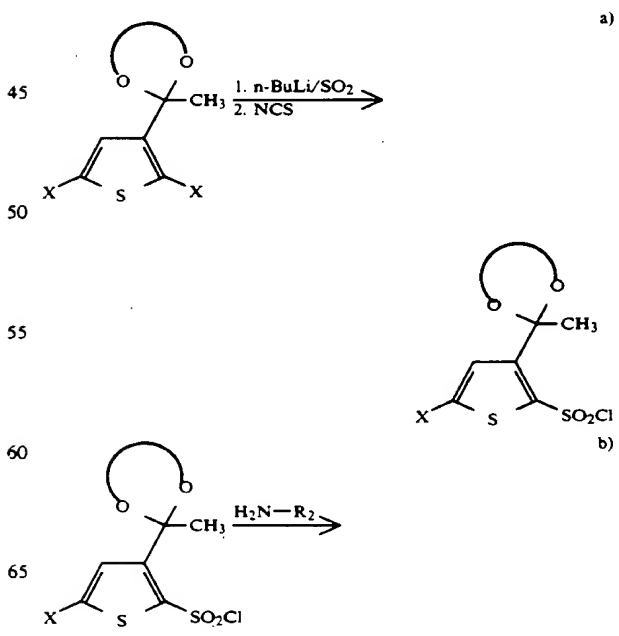


Novel compounds of Structure I wherein R_1 and R_3 are joined in a manner so as to provide fused bicyclic compounds, such as 3,4-dihydro-thieno-1,2-thiazine 1,1-dioxides, can be prepared from the appropriately substituted thiophenesulfonamides according to Equations 3–7. Thiophene ketals of Equation 3a, where X is H or halogen, can be readily prepared by standard methods well known to one skilled in the art from commercially available ketones. Treatment of these ketals by the methods of Equations 1a and 1b above provide the intermediate sulfonyl chloride. The sulfonyl chloride can be reacted with either ammonia to give the primary sulfonamide, or with the desired alkylamine or arylamine to give a secondary sulfonamide (Equation 3b). Alternately, the primary sulfonamide can be prepared from the intermediate sulfinate salt with t[illegible]ylamine-O-sulfonic acid.

Equation 3



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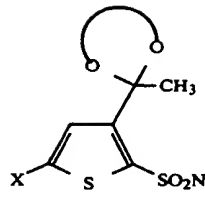
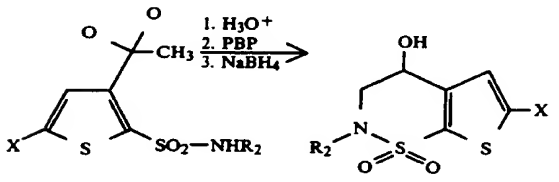


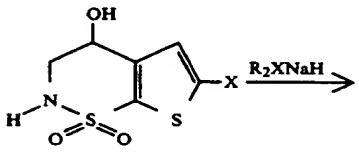
Conversion of these acyclic sulfonamides into the desired thienothiazine compounds can be accomplished using a variety of procedures well known in the art; e.g. acid hydrolysis of the ketal followed by bromination of the ketone and subsequent base catalyzed cyclization of the e-bromoketone (Equation 4).

Equation 4

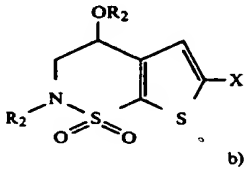


Certain desired bicyclic compounds of Structure I can be readily prepared by a sequence which involves initial alkylation with an appropriate alkyl halide in the presence of a suitable base (Equation 5a) followed by introduction of the sulfamoyl group by procedures analogous to Equations 1a–d, that is metallation of the alkylated product of Equation 4 with a strong organometallic base such as n-butyllithium, followed by treatment with sulfur dioxide to give the intermediate sulfinate salt which is aminated, e.g. by reaction with hydroxylamine-O-sulfonic acid (Equation 5b). Treatment of this intermediate with an appropriate alkyl nitrile in the presence of sulfuric acid provides an amide which upon reduction gives the desired amine [Equation 5c; R′ is lower alkyl (C_{1-4})].

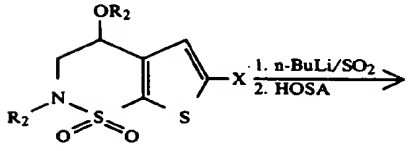
Equation 5



a)



b)



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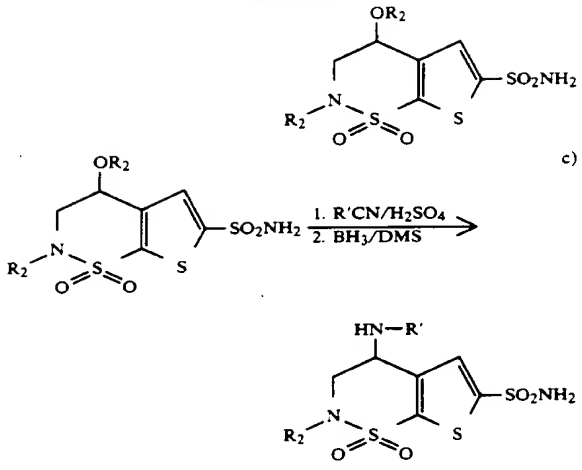
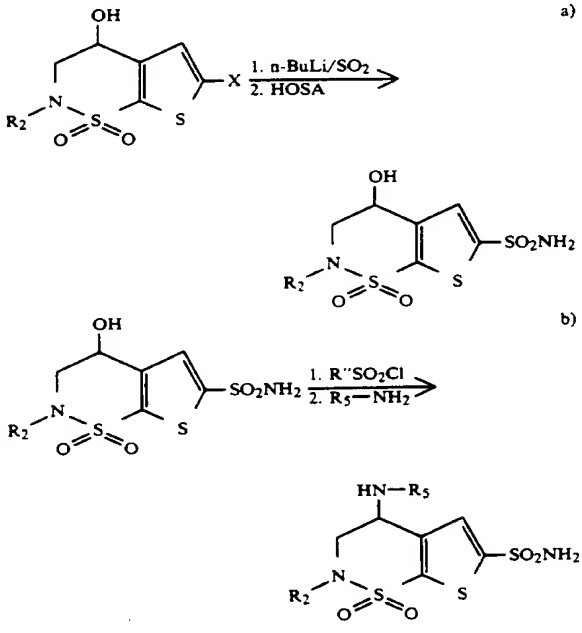


c)

Yet other desirable compounds of Structure I are better prepared according to Equation 6 where the cyclic intermediate from Equation 4 is sulfamoylated (see Equation 5b) at position six (Equation 6a) followed by conversion of the hydroxyl group to a sulfonate ester (e.g. R'' is p-toluyl or methyl) and reaction of this intermediate with the desired alkylamine (Equation 6b).

Equation 6



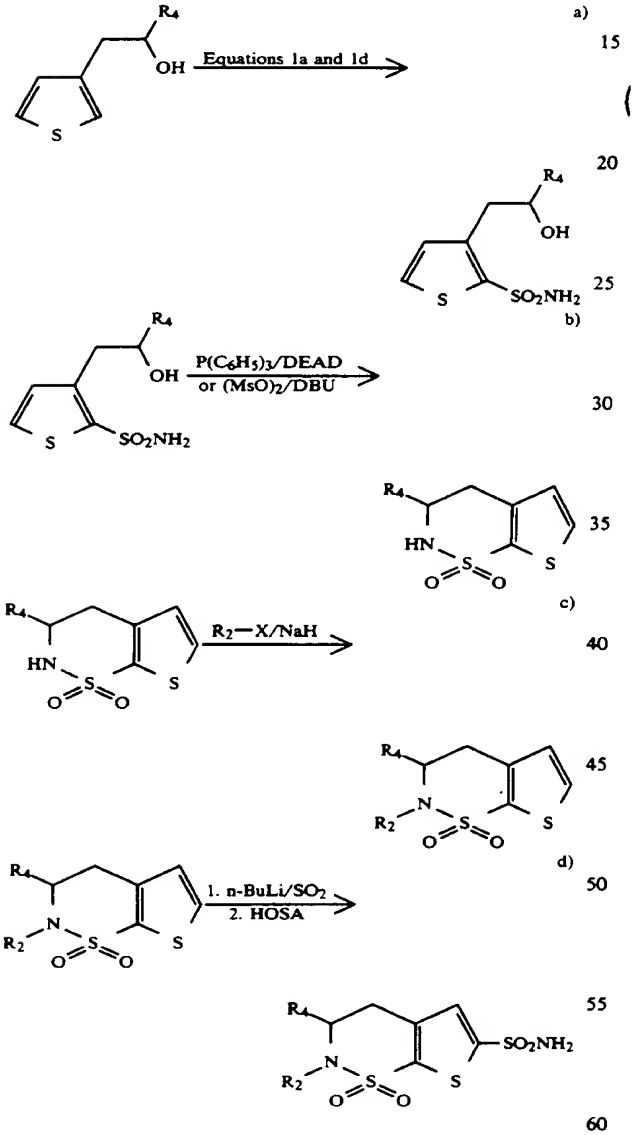
a)

b)

Still other desirable compounds of Structure I can be prepared (Equation 7) from an appropriate thienylethanol; these intermediate alcohols can be readily prepared by procedures well known in the art, e.g. reaction of thienyl-3-acetaldehyde with an appropriate Grignard reagent. Sulfamoylation of such alcohols by the procedures described in Equations 1a and 1d provide exclusively the desired thiophene-2-sulfonamide intermediates of Equation 7a. Cyclization to the desired bicyclic

thienothiazine can be accomplished by procedures known in the art, but preferably cyclization is accomplished using conditions of the Mitsunobu reaction, diethyl azodicarboxylate-triphenylphosphine, or by displacement of a sulfonate ester under basic conditions (Equation 7b). The requisite R_2 group can be introduced using standard alkylation conditions (Equation 7c) and introduction of the primary sulfonamide can be accomplished by procedures similar to those already described in Equations 1a, 1b, and 1d (Equation 7d).

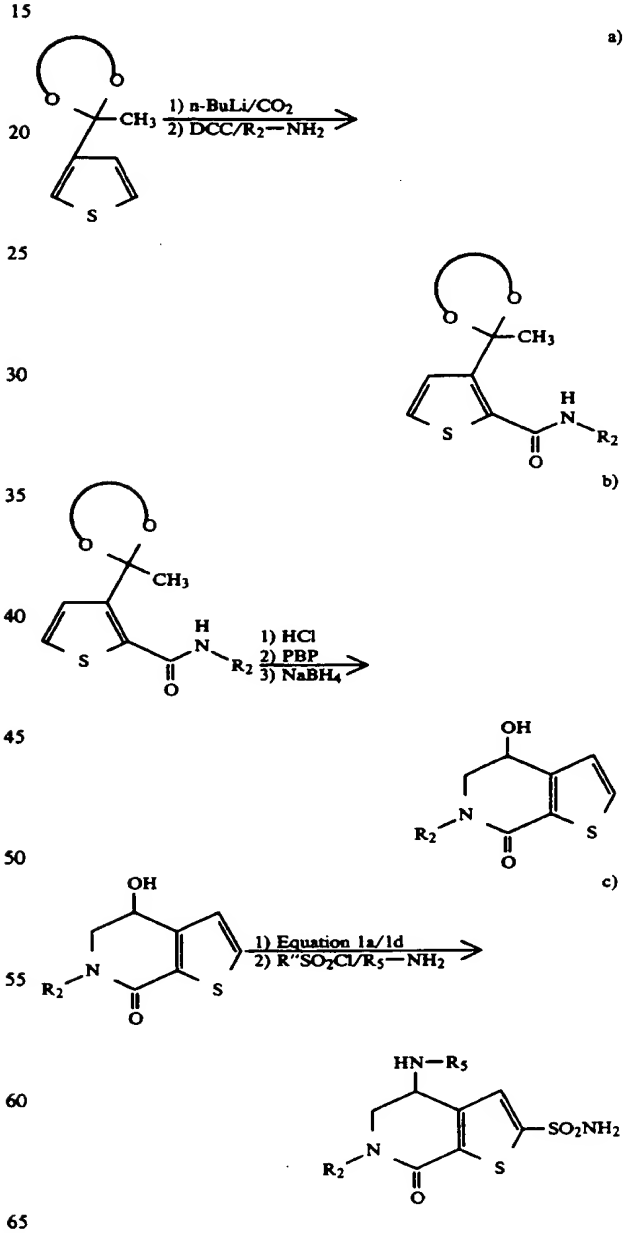
Equation 7



Yet other fused bicyclic compounds of Structure I, such as tetrahydrothieno[2,3-b]pyridine-2-sulfonamides, can be prepared in much the same manner as already described in Equations 2–6. Thiophene ketals (see Equation 3a) are readily metallated by strong organometallic bases and upon subsequent reaction with carbon dioxide provide the lithium carboxylates which upon coupling with ammonia or a desirable amine in the

presence of a suitable activating agent such as dicyclohexylcarbodiimide, provides the primary or secondary thiophene-2-carboxamides, respectively (Equation 8a). Deprotection of the amides followed by bromination provides the α-bromoketones which can be readily cyclized under basic conditions (8b). Introduction of the desirable primary sulfonamide group can be accomplished in a manner analogous to that previously described in Equations 1a, 1b, and 1d. The alcohols can be transformed to amines if desired by initial conversion to an aryl or alkyl sulfonate ester and subsequent treatment with the desired amine (Equation 8c).

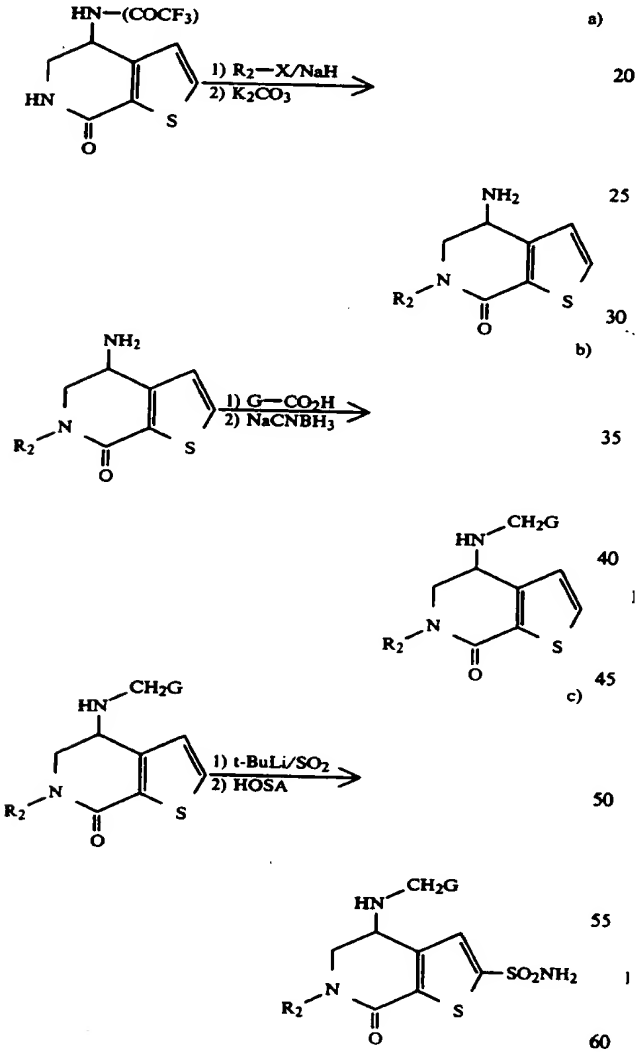
Equation 8



Alternately, such compounds can be prepared by the procedure shown in Equation 9. Alkylation of 4,5,6,7-tetrahydro-4-(trifluoroacetamido)-7-oxo-thieno[2,3-

b]pyridine [Heterocycles, 27, 1637 (1988)] with the requisite R_2 group using standard alkylation procedures followed by hydrolysis of the amide provides the primary amine as shown in Equation 9a. This intermediate primary amine can be selectively transformed to more desirable secondary amines using well known methods of reductive amination, that is treatment with the desired aldehyde and a suitable reducing agent, or reductive alkylation, that is reaction with the requisite carboxylic acid and a suitable reducing agent [Equation 9b; G is H or loweralkyl (C_{1-4})]. Introduction of the primary sulfonamide can be accomplished as previously described in Equations 1a, 1b, and 1d, but preferably using t-butyllithium as the base (Equation 9c).

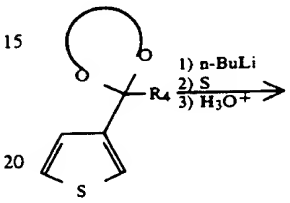
Equation 9

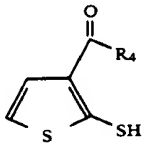


Certain cyclic compounds of Structure I, such as the 2,3-dihydrothienoisothiazoles, can be obtained through the modification of an existing cyclic compound (Equation 10). The metallated ketals of Equation 3 can be readily converted to the desired intermediate mercaptoketones as shown in Equation 10a, and the oxime O-esters of such compounds can be cyclized according

to Equation 5b. Oxidation and subsequent reduction of the thienoisothiazole by procedures well known in the art provides the intermediate cyclic sulfonamides shown in Equation 10c. These cyclic sulfonamides can be substituted on nitrogen utilizing standard alkylation procedures such as demonstrated by Equation 10d. Incorporation of the primary sulfonamide into position five of these examples of Structure I can be accomplished under the basic conditions demonstrated by Equations 1a-d. Equation 10

a)





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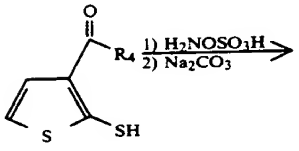

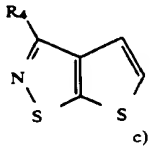

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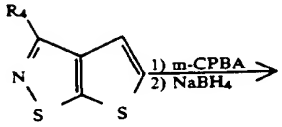

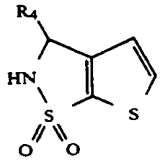

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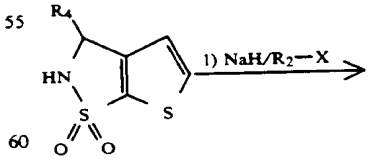

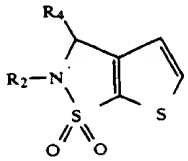

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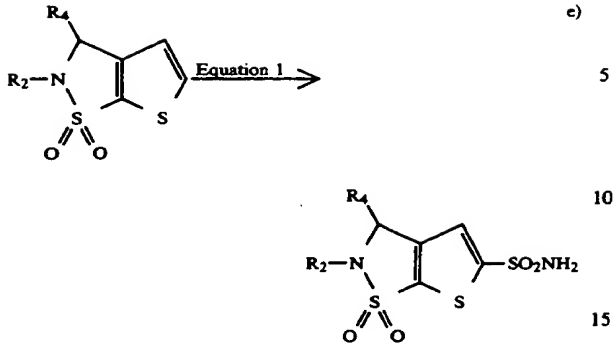
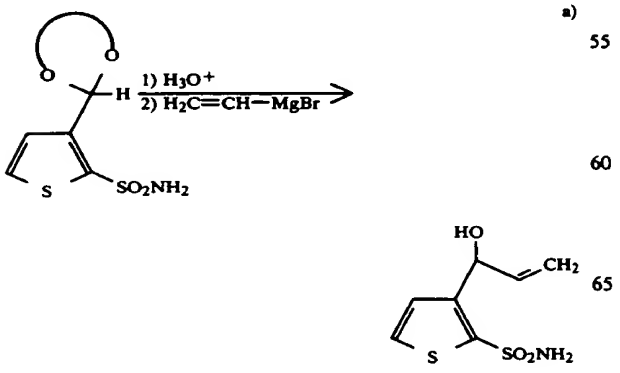
e)



Yet other cyclic compounds of Structure I, such as tetrahydrothienothiazepines, can be prepared from substituted thiophenesulfonamides according to Equation 11. Thiophene acetals can be metallated in the two position with strong metallic bases in a manner similar to that described in Equation 3a for thiophene ketals. These intermediates can be further converted to the thiophene-2-sulfonamides desired for Equation 11a in a manner similar to that described for thiophene ketals by Equations 3a and 1d. Thiophene acetals can be readily converted to the corresponding aldehydes by acid hydrolysis, and reaction of these aldehydes with an olefinic Grignard reagent can provide the olefin intermediates of Equation 11a. The allylic alcohols from Equation 11a can be oxidized to intermediate ketones by a variety of procedures well known to the art, and these ketones can be cyclized upon treatment under basic conditions, such as sodium carbonate, to the cyclic sulfonamides (Equation 11b). The requisite R_1 group can be appended by using standard alkylation reactions (Equation 11c) and these intermediates can be reduced to the requisite alcohols with a suitable reagent, such as sodium borohydride. The alcohols can be transformed to amines by initial conversion to an alkyl or aryl sulfonic acid ester, and subsequent treatment of this intermediate with the desired primary or secondary amine (Equation 11d). Introduction of the primary sulfonamide functionality into the tetrahydrothienothiazepines can be accomplished by procedures similar to those already described in Equations 1a, 1b, and 1d (Equation 11e).

Equation 11

a)



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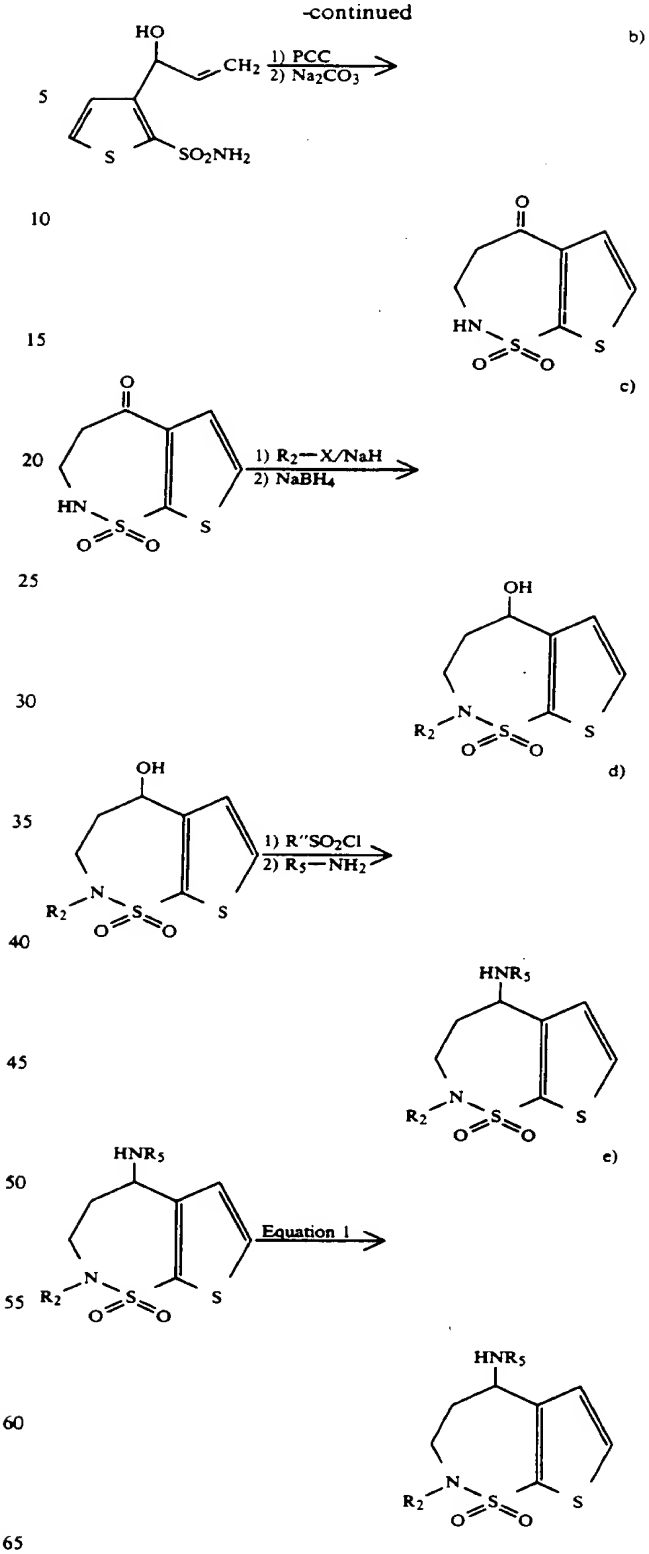
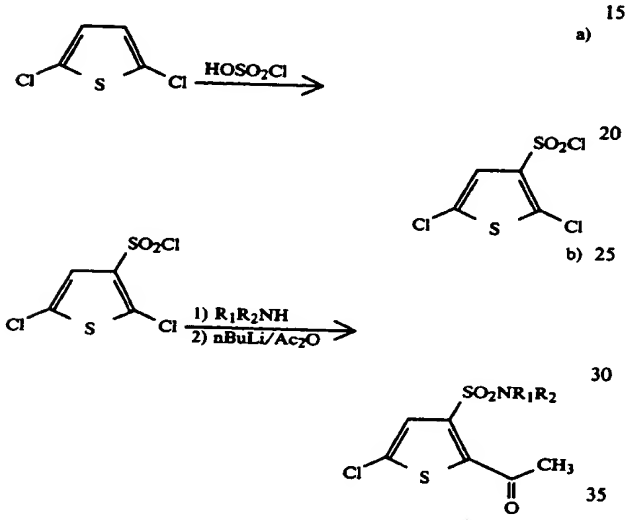


Thienothiazines isomeric to those described in Equations 4–7 can be prepared using a similar route starting from 2,5-dichlorothiophene as shown in Equation 12.

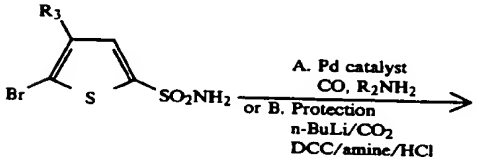
Chlorosulfonation of this starting material followed by amination using methods similar to those described in Equation 2 will provide the desired thiophene-3-sulfonamide (Equation 12a). Subsequent treatment of this intermediate with n-butyllithium at low temperature followed by quenching with acetic anhydride will give rise to the ketone of Equation 12b. This key intermediate can then be converted into the desired novel compounds of Structure I using substantially the same general methods described in Equations 4–6.

Equation 12



Still other desirable compounds of Structure I, such as 5-sulfamoyl-thiophene-2-carboxamides, can be prepared according to Equation 13. Treatment of the readily prepared 5-bromo-thiophene-2-sulfonamides under palladium mediated amidation reaction conditions [see for example *J. Org. Chem.*, 39, 3327 (1974)] in the presence of the desired amine component provides the novel compounds of Structure I. Alternately, 5-bromo-thiophene-2-sulfonamides can be initially protected, such as with the formamidine group, followed by treatment with a strong organometallic base, such as n-butyllithium or LDA, and carbon dioxide to give the intermediate carboxylic acid. Treatment of this intermediate acid with an activiating agent, such as dicyclohexylcarbodiimide or triphenylphosphine triflate, followed by reaction with the desired amine component provides, following deprotection, the desired compounds of Structure I.

Equation 13



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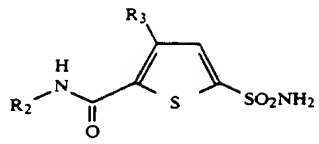
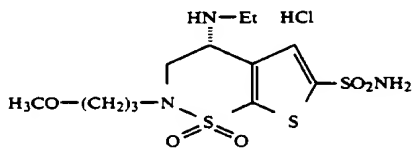


The compounds of Structure I can be incorporated into various types of ophthalmic formulations for delivery to the eye. These compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride and water to form an aqueous, sterile ophthalmic suspensions or solutions. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940 or the like according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated. Ophthalmic solution formulations may be prepared by dissolving the active ingredient in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the active ingredient. Furthermore, the ophthalmic solution may contain a thickener such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like to improve the retention of the medicament in the conjunctival sac.

The compounds are preferably formulated as topical ophthalmic suspensions or solutions, with pH of about 4.5 to 7.8. The compounds will normally be contained in these formulations in an amount of 0.1% to 10% by weight, but preferably in an amount of 0.25% to 5.0% by weight. Thus, for topical presentation 1 to 3 drops of these formulations would be delivered to the surface of the eye 1 to 4 times a day according to the routine discretion of a skilled clinician.

The following examples, which are in no way limiting, illustrate the preparation of selected examples of the novel compounds of Structure I. The compounds set forth in Examples 1, 4–4, 4–5, 4–8, 4–9, 5–2, 5–4, 7, and 8 represent the preferred thiophene sulfonamides of this invention. The compounds represented i n Examples 1, 7, and 8 are most preferred.

Example 1



(+)-4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride

Step A:
3-(2,5,5-Trimethyl-l,3-dioxane-2-yl)-2-thiophenesulfonamide

To a solution of 3-(2,5,5-Trimethyl-l,3-dioxane-2-yl)thiophene (2.5 g, 11.7 mmol) in hexane (30 mL) cooled to 0° C. was added via syringe n-butyllithium in hexane (2.5M, 10.3 mL, 25.7 mmol) over 5 min. The mixture was stirred at 0° C. for 20 min, the ice bath was removed and the stirring was continued for 30 min. At this time a white precipitate formed. The mixture was cooled to −60° C. and THF (20 mL) was added. Sulfur dioxide was then passed through the surface of the mixture for 30 min. The mixture was warmed to ambient temperature and stirred for an additional 15 min. The volatiles were evaporated and to the residue was added water (50 mL) and sodium acetate trihydrate (9.55 g, 70.2 mmol). The solution was cooled on an ice bath and hydroxylamine-O-sulfonic acid (4.62 g, 40.9 mmol) was added. The mixture was stirred at ambient temperature for 1 h, extracted with ethyl acetate (3×100 mL) and the combined extracts were washed with a sodium bicarbonate solution, brine and dried over molecular sieves. Evaporation to dryness gave a viscous liquid (4.93 g), which was chromatographed (silica, eluting with 33% ethyl acetate-hexane) to give a solid (2.47 g, 72%): mp 200°–202° C.

Step B: 3-Acetyl-2-thiophenesulfonamide

A mixture of the compound from Step A (9.45 g, 32.5 mmol) and 1N HCl (100 mL) in THF (100 mL) was heated at reflux for 1 h. The THF was evaporated and the aqueous solution was made basic by the addition of sodium bicarbonate. The mixture was cooled using an ice bath and the precipatiate was filtered, washed with cold water and dried in vacuo to give 5.83 g (88%) of a solid: mp 193°–196° C.

Step C:
3,4-Dihydro-4-hydroxy-2H-thieno[3,2-e]-2-thiazine 1,1-dioxide

The product from Step B (5.73 g, 28.0 mmol) was dissolved in hot THF (200 mL). The solution was cooled to 10° C. and pyridinium bromide perbromide (10.73 g, 33.5 mmol) was added. The mixture was allowed to stir at ambient temperature for 1 h. The volatiles were evaporated and the residue was mixed with water. The precipitate was filtered, washed with cold water and dried in vacuo overnight to give 7.77 g of a solid. A portion of this solid (3.49 g, 12.3 mmol) was suspended in ethanol (100 mL) and treated with sodium borohydride (266 mg, 7.04 mmol). The suspension turned clear after 10 min and was heated at reflux for 1 h. The ethanol was evaporated and the residue was extracted with ethyl acetate, washed with brine and evaporated to give the product (1.80 g, 71%): mp 138°–140° C.

Step D:
2-(3-Bromo)propyl-3,4-dihydro-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine

The product from Step C (8.0 g, 39.0 mmol) was dissolved in anhydrous DMF (100 mL), cooled to −20° C. and sodium hydride (1.87 g, 46.8 mmol) was added. After stirring for five minutes, 1,3-dibromopropane (20 mL, 19.5 mmol) was added and the reaction mixture stirred for 3 hr at 0° C. The reaction mixture was diluted with ice water (100 mL) and this solution was extracted

with ethyl acetate (3×30 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to give a crude product which was purified by column chromatography [silica; CH_3OH/CH_2Cl_2(20:1)] to provide the desired product (10.1 g, 79%) as a syrup.

Step E:

2-(3-Bromo)propyl-4-(1-ethoxy)ethoxy-3,4-dihydro-2H-thieno-[3,2-e]-1,2-thiazine

The product from Step D (10.1 g, 30.1 mmol) and p-toluenesulfonic acid (1.1g) were dissolved in THF (100 mL) and cooled to −20° C. at which point ethylvinyl ether (5.8 mL, 60.2 mmol) was added. This mixture was allowed to warm to 0° C. and kept at this temperature for 1.5 hr followed by dilution with cold ethyl acetate (200 mL). The organic layer was separated, washed with saturated sodium bicarbonate (3×50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated to provide 9.5 g (79%) of crude product which was used in the next step without further purification.

Step F:

4-(1-Ethoxy)ethoxy-3,4-Dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine.

The product from Step E (9.5 g, 23.8 mmol) was dissolved in methanol (200 ml) and sodium methoxide (6.5 g, 119 mmol) was added; the mixture was heated at reflux temperature for 18 hr. Evaporation of the solvent gave the crude product which was dissolved in ethyl acetate (300 mL). This solution was washed with water (3×50 mL) and brine (3×35 mL), dried ($MgSO_4$) and evaporated to provide the crude product which was purified by column chromatography [silica; CH_3OH/CH_2Cl_2(20:1)] to give 6.5 g (78%) of product as a syrup.

Step G:

3,4-Dihydro-4-hydroxy-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide.

The product from Step F (6.5 g, 18.6 mmol) was dissolved in THF (40 mL), cooled to −78° C. and treated sequentially with n-butyllithium, sulfur dioxide, and hydroxylamine-O-sulfonic acid in a manner essentially identical to that described in Example 2, Step D to provide the desired crude product which, after purification by column chromatography, provided 4.1 g (62%) of an amber syrup.

Step H:

3,4-Dihydro-2-(3-methoxy)propyl-4-oxo-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide.

To a solution of the product from Step G (3.8 g, 10.7 mmol) in acetone (40 mL) at room temperature was added Jones reagent [9.7 mL (prepared by dissolving CrO_3 (7 g) in H_2O (50 mL) and adding H_2SO_4 (6.1 mL)]. This mixture was stirred at room temperature for one hour, diluted with ethyl acetate (200 mL) and washed with a 5% solution of sodium bisulfite (2×100 mL) and brine (2×50 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by column chromatography [silica; CH_3OH/CH_2Cl_2(20:1)] to give 2.7 g (70%) of the desired product: mp 115°–117° C.

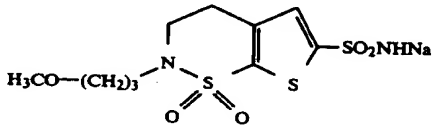
Step I:
(S)-3,4-Dihydro-4-hydroxy-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-di oxide

To a solution of the product of Step H (2.6 g, 7.34 mmol) in THF (30 mL) at −78° C. was added a solution of (+)-β-chlorodiisopinocampheylborane (11.8 g, 36.7 mmol) in THF (10 mL). The reaction mixture was allowed to warm to −20° C. and kept at this temperature for 4 days. Diethanolamine (4.2 mL, 44 mmol) was added to the reaction mixture and the solution stirred for 30 min, diluted with EtOAc (150 mL), washed with water (2×50 mL) and brine (2×50 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by column chromatography [silica; $CH_{30}OH/CH_2Cl_2$(20:1)] to give 2.4 g (92%) of the desired compound as a colorless foam.

Step J:
(+)-4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride

To a solution of the product from Step I (2.4 g, 6.74 mmol) and triethylamine (3.8 mL, 27 mmol) in anhydrous tetrahydrofuran (20 mL) cooled to −20° C. was added tosyl chloride (2.6 g, 13.5 mmol); this mixture was allowed to warm to room temperature and stirred for 18 hr. The reaction mixture was cooled to −60° C. and ethylamine (10 mL) was added and the mixture was again allowed to warm to room temperature. After 18 hr the reaction mixture was diluted with ethyl acetate (200 mL), washed with a saturated aqueous solution of sodium bicarbonate (3×50 mL), dried ($MgSO_4$), and evaporated to give the crude product which was purified by column chromatography [silica; CH_3OH/CH_2Cl_2(20:1)] to give 1.3 g (52%) of the desired amine. The free base was dissolved in ethanol (5 mL) and treated with a 2M solution of hydrochloric acid in ethanol (4 mL) at room temperature. Evaporation of the solvent provided a solid which was recrystallized from methanol: methylene chloride to give 950 mg (34%) of the desired product; mp 175°–177° C.; $[\alpha]_D$+10.35° (C=1.00, H_2O). Analysis. Calculated for $C_{12}H_{22}ClN_3O_5S_3$: C, 34.32; H, 5.28; N, 10.00 Found: C, 34.26; H, 5.23; N, 9.92.

EXAMPLE 2



3,4-Dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide sodium salt

Step A:
3,4-Dihydro-4-hydroxy-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine- 1,1-dioxide

The product from Example 1, Step C (2.0 g, 9.74 mmol) was added to a suspension of sodium hydride (0.4 g, 10.0 mmol, of a 60% suspension in mineral oil) in DMF (30 mL) and the mixture was stirred for 1 hr. then cooled to 20° C. 3-Bromopropyl methyl ether (1.5 g, 9.74 mmol) was added and the mixture was stirred overnight then quenched with water (200 mL), and ex-

tracted with ethyl acetate (4×30 mL). The extracts were combined, washed with water (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure which provided an oil which was purified by column chromatography (silica, gradient: hexane to ethyl acetate) to give 1.7 g (63%) of a clear oil which was not purified further.

Step B:

3,4-Dihydro-2-(3-methoxypropyl)-4-O-phenoxythiocarbonyl-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step A (1.68 g, 6.06 mmol) and DMAP (1.48 g, 12.11 mmol) were dissolved in 1,2-dichloroethane (16 mL) and cooled in an ice bath. Phenoxythiocarbonyl chloride (1.26 mL, 9.09 mmol) was added slowly and the reaction mixture was stirred at room temperature overnight, then quenched with water (40 mL). The mixture was extracted with dichloromethane (3×10 mL) and the extracts were combined, washed with saturated sodium chloride solution, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica, gradient: hexane to 3:1 hexane/ethyl acetate) to give 1.75 g (70%) the desired product as an oil which was used in the next step.

Step C:

3,4-Dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step B (1.75 g, 4.23 mmol) and AIBN (100 mg) were mixed with dry benzene (12 mL) and degassed under nitrogen. The mixture was heated to reflux and tributyltin hydride (1.2 mL, 4.44 mmol) was added rapidly dropwise to maintain a gentle reflux. Heating was continued for 30 min and the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica, gradient: hexane to 3:1 hexane/ethyl acetate) to provide the desired product (1.06 g, 95%) as a clear oil.

Step D:

3,4-Dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide sodium salt

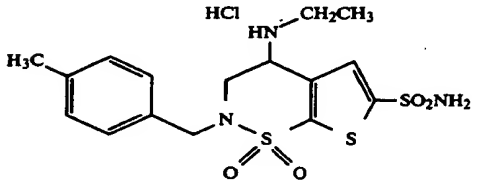
The product form Step C (1.03 g, 3.94 mmol) was dissolved in dry THF (20 mL) and cooled (−65° C.) under nitrogen. n-Butyllithium (2.1 mL of a 2.1M solution in hexanes) was added dropwise and the mixture was stirred for 45 min, then excess sulfur dioxide was introduced into the flask until the solution tested acidic to moist litmus paper. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in water (25 mL) and sodium acetate trihydrate (2.68 g, 19.7 mmol) then hydroxylamine-O-sulfonic acid (1.34 g, 11.8 mmol) were added and the mixture was stirred at room temperature for 16 hr followed by extraction with ethyl acetate (5×5 mL). The extracts were combined, washed with saturated sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica, gradient: 3:1 hexane/ethyl acetate to 7:3 methylene chloride/methanol) which gave the desired product (1.21 g, 69%) as an amber syrup which was converted to the sodium salt as follows: The residue was dissolved in 2N NaOH (1.78 mL, 3.56 mmol), then mixed with ethanol (1.8 mL) and cooled. Ethyl ether was added to the cloud point and the product precipitated from the solution. The solids were collected and

dried to provide the desired product (0.94 g, 73%) as a white solid: mp 169°–170° C. Analysis: Calculated for $C_{10}H_{15}N_2O_5S_3Na$-0.5 H_2O: C, 32.34; H, 4.34; N, 7.54. Found: C, 32.27; H, 4.19; N, 7.42.

By following the above general procedure but using instead 2-bromoethyl methyl ether or 4-bromobutyl methyl ether in Step A the following compounds were prepared.

1. 3,4-Dihydro-2-(2-methoxyethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide, mp 131°–132° C.;
2. 3,4-Dihydro-2-(3-methoxybutyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide sodium salt, mp 244° C.

EXAMPLE 3



4-Ethylamino-3,4-dihydro-2-(4-methylphenyl)methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Step A:

3,4-Dihydro-4-hydroxy-N-(1,1-dimethyl)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

To a solution of the product from Example 1, Step C (6.25 g, 30 mmol) in THF (40 mL) at 0° C. was added p-toluenesulfonic acid (200 mg) and ethyl vinyl ether (10.3 mL, 0.107 mol). The mixture was stirred for 6 hr at 0° C. followed by the addition of an aqueous solution of sodium bicarbonate (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×50 mL). The extracts were combined, washed with brine (30 mL), dried ($MgSO_4$) and evaporated to give an oil which was purified by column chromatography (silica; 30% ethyl acetate/hexane) to give the desired protected intermediate product (10.1 g, 99%). To a solution of this material (9.6 g,28 mmol) in THF (60 mL) was added a solution of n-butyllithium in pentane (20.6 mL of a 2.0M solution) at −78° C. over a period of 20 minutes. After stirring this solution for 45 min, a stream of sulfur dioxide gas was passed over the surface of the solution (20 min). The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 2 hr. The solvent was evaporated to give a residue which was dissolved in methylene chloride (200 mL), cooled to 0° C., and N-chlorosuccinamide (7.4 g, 55 mmol) was added in portions. After one hour the reaction mixture was allowed to warm to room temperature; stirring continued for two more hours, at which point the methylene chloride was removed by evaporation and the residue dissolved in THF (100 mL). This solution was cooled (0° C.) and a solution of t-butylamine (7.8 mL, 75 mmol) in THF (50 mL) was added dropwise followed by stirring for 8 hr at room temperature. After removal of excess amine by evaporation, 2N HCl (10 mL) was added and the reaction mixture stirred at room temperature for 8 hr. Water (50 mL) was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic layers were washed

with brine (30 mL), dried ($MgSO_4$), and evaporated to provide crude product which was purified by column chromatography (silica; 5% methanol/methylene chloride) to give the desired product as a yellow syrup (7.3 g, 72%).

Step B: 3,4-Dihydro-4-hydroxy-N-(1,1-dimethyl)ethyl-2-(4-methylphenyl)methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

The product from Step A (4.0 g, 12 mmol) was dissolved in anhydrous DMF (40 mL) and added to a suspension of sodium hydride (0.58 g of a 60% dispersion in mineral oil, 14.4 mmol) in anhydrous DMF (30 mL) at 0° C.; this mixture was stirred at 0° C. for 3 hr. α-Chloro-p-xylene (2.2 mL, 24 mmol) was added and the solution was allowed to warm to room temperature, stirring continued at this temperature for 72 hr. The DMF was evaporated and the residue was suspended in water (60 mL); this mixture was extracted with ethyl acetate (4×50 mL) and the combined extracts were dried (Na_2SO_4), filtered, and evaporated to give a brown solid (5.12 g, 99%) which was not purified further.

Step C: 4-Ethyl amino-3,4-dihydro-N-(1,1-dimethyl)ethyl-2-(4-methylphenyl)methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

The product from Step B (2,5 g, 7.3 mmol) was dissolved in anhydrous THF (960 mL) under nitrogen. The solution was cooled to 0° C. and p-toluenesulfonyl chloride (2.21 g, 12 mmol) and triethylamine (3.23 mL, 0.23 mol) were added. The mixture was stirred for 16 hr at 0° C. and then cooled to −60° C. Ethylamine (50 mL, 0.76 mol) was condensed into the reaction mixture and the solution was allowed to warm to room temperature and stirred for 72 hr. The solvent was evaporated and the residue was suspended in water (100 mL). The aqueous mixture was extracted with ethyl acetate (5×100 mL) and the combined extracts were dried (Na_2SO_4), filtered, and evaporated to an oil which was purified by column chromatography (silica, gradient: 70% hexane/ethyl acetate to 50% hexane/ethyl acetate) to give a brown oil (1.33 g, 51%).

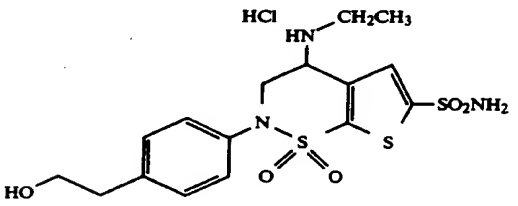
Step D: 4-Ethylamino-3,4-dihydro-2-(4-methylphenyl)methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

The product from Step C (1.3 g, 3 mmol) was dissolved in trifluoroacetic acid (15 mL) and stirred at room temperature for 16 hr. The trifluoroacetic acid was removed by evaporation, ethyl acetate (30 mL) was added and it was also removed by evaporation to give a residue which was suspended in water (30 mL). This mixture was extracted with ethyl acetate (3×30 mL) and the combined extracts were dried (Na_2SO_4), and evaporated to an oil which was purified by column chromatography (silica, 80% ethyl acetate/hexane) to give a white solid (400 mg). This material was dissolved in ethanol (25 mL) and treated with an excess of ethanolic hydrogen chloride for 2 hr; evaporation of the ethanol gave a white solid. This solid was dissolved in water (40 mL), evaporated, and dried to give the desired product (0.41 g, 32%) as a white solid: mp 207°–210° C. Analysis: Calculated for $C_{16}H_{22}ClN_3O_4S_3$-1.5 H_2O: C, 40.10; H, 5.26; N, 8.80. Found: C, 40.35; H, 4.75; N, 8.65.

By following the above general procedure but using the appropriate arylalkyl halide in Step B and either n-propylamine or ethylamine in Step C the following compounds were prepared:

1. 3,4-Dihydro-2-(3-phenylpropyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 124°–127° C.
2. 3,4-Dihydro-2-(4-phenylbutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 120°–125° C.
3. 4-Ethylamino-3,4-dihydro-2-(2-thienyl)methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 182°–184° C.

EXAMPLE 4



4-Ethylamino-3,4-dihydro-2-[4-(2-hydroxyphenyl)phenyl]-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Step A: 3-Acetyl-2-(phenylmethyl)thio-5-chlorothiophene

A mixture consisting of thiourea (858.4 g, 11.28 mol), benzyl bromide (1,930 g, 11.28 mol), THF (9000 ml), and water (3000 ml) was heated at reflux temperature for 2 hr followed by cooling to 50° C. To this solution was added 3-acetyl-2,5-dichlorothiophene (2000 g, 10.25 mol) and an aqueous solution of sodium hydroxide (2,200 g of 50% NaOH diluted to 3000 ml); this mixture was heated at reflux temperature for 4 hr, cooled to room temperature, and the two layers separated. The organic layer was diluted with ethyl acetate (6000 ml) and washed with water (3×2000 ml) and saturated aqueous sodium chloride, dried ($MgSO_4$), and the solvent evaporated to give a residue which was triturated with hexane. This solid was collected by filtration and dried to give the desired product (2,550 g, 88%): mp 86°–88° C.

Step B: 3-Acetyl -5-chloro-N-[4-(2-hydroxyethyl)phenyl]-thiophene-2-sulfonamide

The product from Step A (15 g, 0.058 mol) was dissolved in glacial acetic acid (150 mL), water (15 mL) was added and the solution cooled to 3° C. Chlorine gas was slowly passed through the solution until the temperature reached 15° C. at which point the mixture was cooled to 5° C. before the addition of chlorine was continued; this sequence was repeated four times. The reaction mixture was poured into ice water (400 mL) and extracted with methylene chloride (3×200 mL). The combined extracts were washed with cold saturated aqueous $NaHCO_3$ (2×250 mL), dried ($MgSO_4$), and evaporated. The sulfonyl chloride obtained from this procedure was dissolved in THF (50 mL) and added to a solution of 4-(hydroxyethyl)aniline (16 g, 0.116 mol) in THF (100 mL); this mixture was stirred for 2 days followed by evaporation of the solvent. The residue was suspended in 1M HCl and extracted with methylene chloride (2×100 mL). The combined ex-

tracts were washed with 1N HCl and then dried ($MgSO_4$), filtered, and evaporated to a syrup which was purified by column chromatography (silica, gradient: 3% to 5% ethanol/methylene chloride) to provide a yellow solid (11.6 g, 56%): mp 112°-116° C.

Step C:

6-Chloro-3,4-dihydro-2-[4-[2-(t-butyldiphenylsiloxy)ethyl]phenyl]-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step B (11.5 g, 0.032 mol) was added to DMF (100 mL) containing imidazole (5.44 g, 0.08 mol) and t-butyldiphenylsilyl chloride (9.34 mL, 0.035 mol) and stirred at room temperature for 18 hr. The reaction mixture was evaporated to dryness and the residue was suspended in methylene chloride and filtered. The filtrate was concentrated and chromatographed (silica, methylene chloride) to provide a solid which was dissolved in THF (200 mL) and cooled to 5° C. A solution of pyridinium bromide perbromide (11.23 g, 0.035 mol) in THF (50 mL) was added dropwise and this mixture was stirred at 5° C. for 1 hr, at ambient temperature for 1 hr, and then evaporated to dryness. The residue was suspended in ethanol (150 mL) and cooled to 5° C. followed by the addition of sodium borohydride (3.59 g, 95 mmol). The reaction mixture was maintained at room temperature for 1 hr and then heated at reflux temperature for 1.5 hr. Water was carefully added and the ethanol evaporated. The aqueous mixture was neutralized and extracted with ethyl acetate (2×200 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by column chromatography (silica, 15% ethyl acetate/hexane) to provide an amber syrup (8.2 g, 44%).

Step D:

2-[4-[2-(t-Butyldiphenylsiloxy)ethyl]phenyl]-3,4-dihydro-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

The product from Step C (8.2 g, 14 mmol) was dissolved in dry THF (50 mL) along with p-toluenesulfonic acid (0.5 g) and the solution cooled to 5° C. with an ice bath. Ethyl vinyl ether (2.62 mL, 27 mmol) was added and the reaction mixture was stirred for 0.5 hr. Saturated aqueous sodium bicarbonate (75 mL) was added to the reaction mixture followed extraction with ethyl acetate (2×50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by column chromatography (silica, 20% ethyl acetate/hexane) to provide an oil (7.62 g, 83%). This material was dissolved in dry THF (70 mL) under nitrogen and cooled to −65° C. n-BuLi (15 mL of a 1.76M solution, 26 mmol) was added dropwise, after 0.5 hr the reaction mixture was treated with sulfur dioxide until the dark solution turned yellow, stirring continued for 0.5 hr at room temperature. Evaporation of the solvent provided a residue which was suspended in water (50 mL) containing sodium acetate (7.7 g, 57 mmol) and hydroxylamine-O-sulfonic acid (3.88 g, 34 mmol). This mixture was stirred at room temperature for 18 hr and then treated with 6N HCl (5 mL) for 3 hr followed by extraction with ethyl acetate (2×60 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by column chromatography (silica, gradient: 4% to 5% ethanol/methylene chloride)

to give the desired product (1.78 g, 24%) as an amber syrup.

Step E:

4-Ethylamino-2-[4-[2-(t-butyldiphenylsiloxy)ethyl]-phenyl]-3,4-dihydro-2H-thieno-[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

The product from Step D (1.77 g, 2.75 mmol) was dissolved in dry THF (15 mL) containing triethylamine (1.54 mL, 11 mmol) and cooled to 5° C. p-Toluenesulfonyl chloride (1.05 g, 5.5 mmol) was added and the mixture stirred at 5° C. for 4.5 hr. An excess of ethylamine was condensed into the reaction mixture which was stirred at ambient temperature for 18 hr and then evaporated to dryness. The residue was suspended in water and this mixture was extracted with ethyl acetate (2×50 mL). The combined extracts were dried ($NaSO_4$) and purified by column chromatography (silica, 3.5% ethanol/methylene chloride) to provide 0.8 g (44%) of a solid: mp 66° C.

Step F:

4-Ethylamino-2-[4-(2-hydroxyethyl)phenyl]-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

The product from Step E (0.7 g, 1.0 mmol) was dissolved in methanol (15 mL), tetra-n-butylammonium fluoride (12 mL of a 1.0M solution in THF, 12 mmol) was added, and the solution stirred at room temperature for 4 days. The reaction mixture was evaporated and the residue suspended in water; this mixture was basified with sodium bicarbonate and extracted with ethyl acetate 3×30 mL). The combined extracts were dried (molecular Sieves) and evaporated to a residue which was purified by column chromatography (silica, 8% ethanol/methylene chloride). The isolated material was treated with an excess of 1.5N ethanolic/hydrogen chloride. Evaporation provided a syrup which crystallized from isopropanol to give the desired product (0.22 g, 45%): mp 156°–159° C. Analysis: Calculated for $C_{16}H_{22}ClN_3O_5S_3$: C, 39.54; H, 4.98; N, 8.64. Found: C, 39.73; H, 5.08; N, 8.58.

By using modifications of the above procedure and using either aniline or 4-n-butylaniline in Step B and n-propylamine in Step E the following compounds were prepared.

1. 2-(4-n-Butyl phenyl)-3,4-dihydro-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 148°–152° C.;
2. 3,4-Dihydro-2-phenyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide tartrate, mp 123°–126° C.

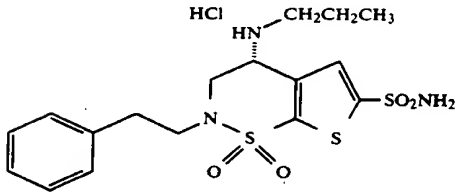
By following the above general procedure but treating the product of Step D in a manner analogous to that described in Example 1, Steps H and I, the desired enantiomer (S configuration) of the product of Step D can be prepared. By treatment of this enantiomer as described in Steps E and F of the current Example the following compound can be prepared.

3. (R)-4-Ethylamino-2-[4-(2-hydroxyethyl)phenyl]-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

By using modifications of the above procedure but replacing 4-(2-hydroxyethyl)-aniline with the appropriately substituted aniline in Step B, and using either ethylamine or n-propylamine in Step E, the following compounds can be prepared.

4. (R)-4-Ethylamino-2-(4-methoxy-phenyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
5. (R)-4-Ethylamino-2-(4-hydroxy-phenyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
6. (R)-3,4-Dihydro-2-(4-methoxy-phenyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
7. (R)-3,4-Dihydro-2-(4-methoxy-phenyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
8. (R)-4-Ethylamino-3,4-dihydro-2-(3-methyoxy-phenyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
9. (R)-4-Ethylamino-3,4-dihydro-2-(3-methyoxy-phenyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
10. (R)-3,4-Dihydro-2-(3-methoxy-phenyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
11. (R)-3,4-Dihydro-2-(3-methoxy-phenyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

EXAMPLE 5



R-(+)-3,4-Dihydro-2-(2-phenylethyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

R−(+)-3,4-Dihydro-2-(2-phenylethyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

The following procedure is the invention of D. Dean et al. which is described and claimed in a concurrently filed, commonly assigned application.

Step A: 3-Acetyl-5-chloro-thiophene-2-sulfonamide

A 50-L, 5-necked flask equipped with a mechanical stirrer, a thermometer, and an 8 mm i.d. gas inlet tube was charged with the product from Example 4, Step A (1 kg, 3.54 mol) and ethyl acetate (20 L) and the pale yellow solution was cooled to 2° C. over 30 minutes using an ice-water bath. While the temperature was maintained below 7° C., chlorine gas was bubbled into the stirred solution, checking the reaction progress by TLC every 10 minutes. The reaction was complete after 30 minutes. Air was bubbled vigorously into the dark orange solution for 1 hour to purge excess chlorine, after which time the temperature was −2° C. While keeping the temperature below 10° C., ammonia was bubbled into the solution until TLC analysis indicated consumption of the intermediate sulfenyl chloride was complete. This required 1 hour and the addition of 120 grams of ammonia. The cold bath was removed and the mixture was again purged with air for 1 hour to remove excess ammonia. Water (5 L) and sodium tungstate dihydrate (583 g, 1.77 mol) were added to the orange suspension. 30% Hydrogen peroxide (7.2 L) was added

from an additional funnel over 15 minutes, causing the temperature to rise to 15° C. The mixture was warmed to 20° C. over 30 minutes and then was stirred vigorously at ambient temperature for 15 hours without external temperature control. Water (5 L) was added, and the phases were split. The organic phase was washed sequentially with saturated aqueous sodium chloride (5 L), 10% aq. sodium bisulfite (5 L), saturated aqueous sodium chloride (5 L), 10% aq. sodium bicarbonate (10 L), and saturated aqueous sodium chloride (10 L). It was then dried over sodium sulfate (1 kg), filtered, and stripped of solvent by rotary evaporation. The residual solid was triturated with t-butyl methyl ether (3 L) and the mixture was chilled for 15 minutes. The solid was collected by filtration, washed with t-butyl methyl ether (1 L), and dried in air at ambient temperature to give the desired product (666 g, 79%): mp 178°–179° C.; Analysis. Calculated for $C_6H_6ClNO_3S_2$: C, 30.06; H, 2.52; N, 5.84; S, 26.75. Found: C, 30.19; H, 2.51; N, 5.80; S, 26.70.

Step B:
3-(2-Bromoacetyl)-5-chloro-thiophene-2-sulfonamide

A 50-L, 5-necked flask equipped with a mechanical stirrer, a thermometer, and a 1 L addition funnel was charged with the product from Step A (1.087 kg, 4.55 mol) and ethyl acetate (22 L) . The pale yellow suspension was cooled to 1° C. over 45 minutes using an ice-water bath and 90% pyridinium bromide perbromide (1.305 kg, 3.67 mol) was added in one portion. Sulfuric acid (544 mL) was added via the addition funnel over 10 minutes causing the temperature to rise to 5° C. The reaction mixture was stirred and, after 1 hour, TLC analysis indicated complete reaction. Thirty minutes later, water (5 L) was added and the mixture was stirred for 5 minutes before the phases were split. The organic phase was washed with saturated aqueous sodium chloride until the pH of the wash was 3 (4×5 L), dried over sodium sulfate (1 kg), filtered, and stripped of solvent by rotary evaporation. The residue was triturated with methylene chloride (2 L) and chilled for 15 minutes before the solid was collected by filtration, washed with cold methylene chloride (2 L), and dried to give the desired product (1.041 kg, 72%): mp 147°–148° C. Analysis. Calculated for $C_6H_5BrClNO_3S_2$: C, 22.62; H, 1.58; N, 4.40; S, 20.13. Found: C, 22.66; H, 1.60; N, 4.35; S, 20.12.

Step C:
(S)-6-Chloro-3,4-dihydro-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

A 50-L, 5-necked flask equipped with a mechanical stirrer and a thermometer was flushed with nitrogen overnight. Working under nitrogen, the flask was charged with the product from Step B (855 g, 2.68 mol) and t-butyl methyl ether (MTBE, 12.5 L). The stirred suspension was cooled to −40° C. using a dry-ice/2-propanol bath and (+)-β-chlorodiisopino-campheylborane (4.5 L of a 1.2M solution in MTBE, 5.4 mol) was added via a cannula over 30 minutes, causing the temperature to rise to −32° C. The reaction mixture was maintained between −25 to −20° C. for 3.5 hours. The mixture was warmed to 0° C. and 1M sodium hydroxide (11 L) was added from an addition funnel over 10 minutes, causing the temperature to rise to 22° C. The biphasic mixture was stirred vigorously at ambient temperature for 2 hours, after which TLC analysis indicated complete cyclization. The phases were split, and

the dark aqueous layer was extracted with t-butyl methyl ether (3 L), acidified to pH 1 using concentrated hydrochloric acid, and extracted with ethyl acetate (2×4 L).

The combined ethyl acetate extracts were washed with saturated aqueous sodium chloride (3 L), dried over sodium sulfate (1 kg), filtered, and concentrated to a volume of about 1 liter by rotary evaporation, at which point toluene (2 L) was added. As the remainder of the ethyl acetate was removed, the product crystallized from toluene. It was collected by filtration, washed with toluene (2 L) and methylene chloride (2 L), and dried in air at ambient temperature (498 grams 77%): mp 126°–127° C.; $[\alpha]^{25}_D$ −5.9° (c=1, CH_3OH). Analysis. Calculated for $C_6H_6ClNO_3S_2$: C, 30.06; H, 2.52; N, 5.84. Found: C, 30.14; H, 2.56; N, 5.80.

Step D:

(S)-6-Chloro-3,4-dihydro-4-hydroxy-2-(2-phenylethyl)-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step C (1.5 g, 6.2 mmol) was added to a suspension of potassium carbonate (2.14 g, 15.5 mmol) in ethanol (25 mL) and phenethyl bromide (2.1 mL, 15.4 mmol) was added in three equal portions over a 24 hr period; stirring continued for 64 hr. The reaction mixture was evaporated and the residue suspended in water which was extracted with ethyl acetate (30 mL). The organic layer was dried ($MgSO_4$) and evaporated to a residue which was partially purified by column chromatography (silica, 3% ethanol/methylene chloride) to give 2.16 g of crude product (consisting of a 1:2 mixture of phenethyl bromide and the desired product) as a yellow oil; this material was used in the next step without further purification.

Step E:

(S)-3,4-Dihydro-4-hydroxy-2-(2-phenylethyl)-2H-thieno[3,2-e]-1,2thiazine-6-sulfonamide 1,1-dioxide

The product from Step D (1.36 g, 3.96 mmol) was dissolved in dry THF (25 mL) along with p-toluenesulfonic acid (0.11 g, 0.6 mmol) and the solution cooled to 5° C. at which point ethyl vinyl ether (1.16 mL, 12.1 mmol) was added. After stirring this mixture for 40 min, saturated aqueous sodium bicarbonate (15 mL) was added followed by extraction with ethyl acetate (40 mL). The organic layer was dried (Na_2SO_4), evaporated, and the residue dissolved in THF (40 mL) under nitrogen. The solution was cooled to 60° C. and n-BuLi (4.1 mL of a 1.76M solution, 7.2 mmol) was added dropwise followed by stirring for 30 min and the introduction of sulfur dioxide until the green solution turned yellow. The cooling bath was removed and the reaction mixture stirred for 1 hr.

Evaporation of the solvent provided a residue which was suspended in water containing sodium acetate (4.89 g, 36 mmol) and hydroxylamine-O-sulfonic acid (2.73 g, 24 mmol); this mixture was stirred for 5 hr. The reaction mixture was acidified to pH 1 with 6N HCl and stirred at room temperature for 18 hr followed by extraction with ethyl acetate (2×50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by column chromatography (silica, 5% ethanol/methylene chloride) to give the desired product as an oil which crystallized upon standing (1.14 g, 75%): mp 117°–119° C.

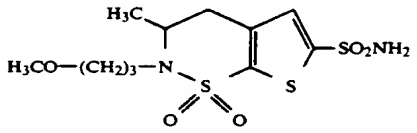
Step F:
R-(+)-3,4-Dihydro-2-(2-phenylethyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

The product from Step E (1.1 g, 2.80 mmol) was dissolved in THF (20 mL) containing triethylamine (1.58 mL, 11.3 mmol) and cooled to 5° C. p-Toluenesulfonyl chloride (1.07 g, 5.6 mmol) was added in small portions and the reaction mixture stirred for 4 hr at 5° C. The ice bath was removed and n-propylamine (30 mL) was added; this mixture was allowed to warm to room temperature and maintained at this temperature for 18 hr. The solvent was evaporated and the residue was extracted with ethyl acetate (4×25 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (3×25 mL), dried (Na_2SO_4), and evaporated to an oil which was purified by column chromatography (silica, 3% ethanol/methylene chloride) to give 0.62 g (52%) of the free base. This material was converted to the hydrochloride salt by treatment with ethanolic hydrogen chloride; recrystallization from ethanol/ether gave 0.55 g (42%) of the title compound as a white solid: mp 120° C.; $[\alpha]_D$+13.6 (c=1.02, CH_3OH). Analysis: Calculated for $C_{17}H_{24}ClN_3O_4S_3$: C, 43.81; H, 5.19; N, 9.02. Found: C, 44.09; H, 5.31; N, 8.78.

By using modifications of the above procedure and replacing phenethyl bromide with the appropriately substituted benzyl halide in Step D, the following compounds can be prepared.

1. (R)-4-Ethylamino-3,4-dihydro-2-(4-methoxyphenylmethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
2. (R)-4-Ethylamino-3,4-dihydro-2-(4-hydroxyphenylmethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
3. (R)-4-Ethylamino-3,4-dihydro-2-(3-methoxyphenylmethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
4. (R)-4-Ethylamino-3,4-dihydro-2-(4-hydroxyphenylmethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

EXAMPLE 6



3,4-Dihydro-2-(3-methoxypropyl)-3-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

Step A: 3-(2-Hydroxypropyl)thiophene-2-sulfonamide

To a solution of 3-(2-hydroxypropyl)thiophene (2.95 g, 20.77 mmol) in THF (25 mL) at −78° C. was added n-butyllithium (18.3 mL of a 2.5M solution, 45.69 mmol). This mixture was stirred at −78° C. for 1 hr and sulfur dioxide was added until the solution maintained a pH of 3. The reaction mixture was warmed to room temperature, stirred for 30 min, and evaporated to a residue which was dissolved in water (25 mL). Sodium acetate (5.1 g, 62.31 mmol) and hydroxylamine-O-sulfonic acid (7.0 g, 62.31 mmol) were added, the mixture stirred at room temperature for 18 hr, and the pH was adjusted to 8 with sodium bicarbonate. This solution

was extracted with ethyl acetate (2×200 mL), the extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by column chromatography (silica, 50% hexane/ethyl acetate) to give 1.9 g (42%) of the desired product.

Step B:
3,4-Dihydro-3-methyl-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

Triphenylphosphene (3.6 g, 13.76 mmol) and diethyl azodicarboxylate (2.2 mL, 13.76 mmol) were dissolved in THF (10 mL) and cooled to 0° C. To this was added a solution of the product from Step A (1.9 g, 8.6 mmol) in THF (10 mL) and the mixture was stirred at 0° C. for 3 hr. The solvent was evaporated and the residue dissolved in ethyl acetate (100 mL); this solution was washed with water (2×50 mL) and brine (2×50 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by column chromatography (silica, 1:2 hexane/ethyl acetate) to give the desired product (995 mg, 57%).

Step C:
3,4-Dihydro-2-(3-methoxypropyl)-3-methyl-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step B (800 mg, 3.94 mmol) was dissolved in DMF (10 mL) and the solution was cooled to −20° C. Sodium hydride (236 mg of an oil dispersion, 5.91 mmol) was added followed by 3-methoxypropyl bromide (1.8 mL, 11.82 mmol) and this mixture was warmed to 0° C. and stirred for 4 hr. The reaction mixture was poured into ice/water (50 mL) and extracted with ethyl acetate (2×100 mL). The combined extracts were washed with water (2×50 mL) and brine (2×50 mL), dried ($MgSO_4$) and evaporated to an oil which was purified by column chromatography (silica, 10% methanol/methylene chloride) to give the desired product (890 mg, 82%).

Step D:
3,4-Dihydro-2-(3-methoxypropyl)-3-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

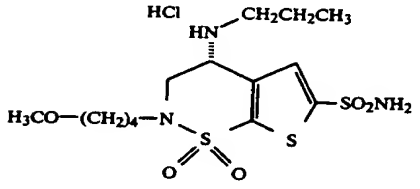
To a solution of the product from Step C (890 mg, 3.23 mmol) in THF (8 mL) at −78° C. was added n-butyllithium (2.0 mL of a 2.5M solution, 4.85 mmol). This mixture was stirred at −78° C. for 40 min and sulfur dioxide was added until the solution maintained a pH of 3. The reaction mixture was warmed to room temperature, stirred for 30 min, and evaporated to a residue which was dissolved in water (20 mL). Sodium acetate (795 mg, 9.69 mmol) and hydroxylamine-O-sulfonic acid (1.0 g, 9.69 mmol) were added, the mixture stirred at room temperature for 18 hr, and the pH was adjusted to 8 with sodium bicarbonate. This solution was extracted with ethyl acetate (2×100 mL), the extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by column chromatography (silica, 5:1 methanol/methylene chloride) to give the desired product. Recrystallization from methylene chloride gave a white solid (320 mg, 29%): mp 140° C. Analysis: Calculated for $C_{11}H_{18}N_2O_5S_3$: C, 37.27; H, 5.12; N,7.90. Found: C, 37.38; H, 5.18; N, 7.86.

By following the above general procedure but substituting the appropriate alkyl halide in Step C the following compounds were prepared:

1. 3,4-Dihydro-2,3-dimethyl-2H-thieno[3,2-e]-2-thiazine-6-sulfonamide 1,1-dioxide, mp 173°–175° C.;

2. 3,4-Dihydro-2-(2-methoxyethyl)-3-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide, mp 106°–108° C.

EXAMPLE 7



R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Step A: N-(1,1-Dimethylethyl)-3,4-dihydro-4-hydroxy-2-(4-methoxybutyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

The product from Example 3, Step A (8.75 g, 0.26 mol) was dissolved in DMF (25 mL) and the solution was cooled to −0° C. Sodium hydride (1.56 g of an oil dispersion, 0.03 mol) was added, stirred for 30 min, and then 4-methoxybutyl bromide (8.6 g,0.052 mol) in DMF (15 mL) was added; this mixture was warmed to room temperature and stirred for 15 hr. A saturated aqueous solution of ammonium chloride (20 mL) was added and the mixture was extracted with ethyl acetate (5×50 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated to an oil which was purified by column chromatography (silica, gradient: 50% to 60% ethyl acetate/hexane) to give the desired product (9.5 g, 86%) as a yellow oil.

Step B: N-(1,1-Dimethylethyl)-3,4-dihydro-2-(4-methoxybutyl)-4-oxo-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

To a solution of the product from Step A (9.5 g, 0.022 mol) in acetone (20 mL) at −10° C. was added freshly prepared Jones reagent (10 mL) and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated and saturated aqueous sodium bicarbonate was added until the pH of the solution was 6. The aqueous mixture was extracted with ethyl acetate (4×50 mL). The combined extracts were washed with brine (2×10 mL), dried ($MgSO_4$) and evaporated to provide a yellow solid (7.5 g, 78%).

Step C: (S)-N-(1,1-Dimethylethyl)-3,4-dihydro-4-hydroxy-2-(4-methoxybutyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

To a solution of (+)-β-chlorodiisopinocamphenylborane (28.01 g, 0.087 mol) in THF (60 mL) at −20° C. was added a solution of the product from Step B (7.4 g, 0.017 mol) in THF (90 mL); this mixture was stirred for 40 hr while maintaining this temperature. Diethanolamine (9.13 g, 0.087 mol) was added to the reaction mixture which was allowed to warm to room temperature and stirred at this temperature for 2 hr. Evaporation of the THF gave a residue which was dissolved in ethyl acetate (100 mL); this solution was washed with water (100 mL). The aqueous layer was separated and extracted with ethyl acetate (3×50 mL). The ethyl acetate extracts were combined, washed with brine

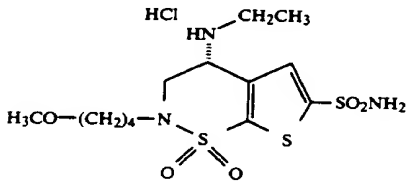
(2×20 mL), dried ($MgSO_4$), and evaporated to a residue which was purified by column chromatography (silica, 60% ethyl acetate/hexane) to give an oil (6.4 g, 86%).

Step D:

R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

To a solution of the product from Step C (5.4 g,0.013 mol) in THF (40 mL) at 0° C. was added triethylamine (5.38 g, 0.053 mol) followed by p-toluenesulfonyl chloride (5.07 g,0.027 mol) and the mixture was stirred for 2 hr. The reaction mixture was divided into two equal volumes, one of which was treated with propylamine (15 mL) at 0° C. for 15 hr. The excess propylamine was evaporated and the solution diluted with water (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated to a crude product which was purified by column chromatography (silica, gradient: 50% to 70% ethyl acetate/hexane). The free base was dissolved in ethanol (10 mL) and treated with ethanolic hydrogen chloride. Evaporation gave a solid which was recrystallized from isopropanol to give the desired product as a white solid (1.4 g, 26%): mp 183°–185° C.; $[\alpha]_D$+27.2° (c=0.43, CH_3OH). Analysis: Calculated for $C_{14}H_{26}ClN_3O_5S_3$-0.5 H_2O: C, 36.79; H, 5.95; N, 9.19. Found: C, 37.08; H, 6.34; N, 8.82.

EXAMPLE 8



R-(+)-4-Ethylamino-3,4-dihydro-2-(4-methoxybutyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

The second portion of the intermediate tosylate prepared in Example 7, Step D was treated with ethylamine (18 mL) at 0° C. for 15 hr. By proceeding in a manner analogous to that already described in Example 7, Step D the title compound was obtained (2.4 g, 46%): mp 129°–130° C.; $[\alpha]_D$+23.6° (c=0.49, CH_3OH). Analysis. Calculated for $C_{13}H_{24}ClN_3O_5S_3$: C, 35.97; H, 5.57; N, 9.68. Found: C, 35.80; H, 5.84; N, 9.41.

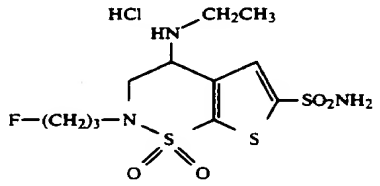
Using modifications of the procedures described above and in Examples 7 but substituting the appropriate alkyl halide in Step A and the desired alkylamine in Step D the following compounds were prepared:

1. R-(+)-4-Ethylamino-3,4-dihydro-2-(6-hydroxyhexyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 200°–201° C;
2. R-(+)-4-Allylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, 202°–205° C.;
3. R-(+)-3,4-Dihydro-2-(4-hydroxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 197°–198° C.;

4. R-(+)-3,4-Dihydro-2-(2-methylpropyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 163°–165° C.;
5. R-(+)-4-Ethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 170° C.;
6. R-(+)-4-Cyclopropylmethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 162°–164° C.
7. R-(+)-4-Ethylamino-3,4-dihydro-2-(3-methoxybutyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 207°–209° C.;
8. R-(+)-3,4-Dihydro-2-(3-methoxypropyl)-4-(2-methoxyethyl)amino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 185°–187° C.;
9. R-(+)-3,4-Dihydro-2-(3-methoxybutyl)-4-n-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 156°–158° C.;
10. R-(+)-4-Ethylamino-3,4-dihydro-2-(4-hydroxybutyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 130° C.

Using modifications of the procedures described above and in Examples 7 but substituting the appropriate alkyl halide in Step A and the desired alkylamine in Step D the following compound can be prepared:

11. (R)-3,4-Dihydro-2-(3-hydroxypropyl)-4-(2-methylpropyl)amino-2-H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride.



4-Ethylamino-2-(3-fluoropropyl)3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Step A:

2-(3-Fluoropropyl)-3,4-dihydro-4-hydroxy-N-(1,1-dimethylethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

The product from Example 3, Step A (1.52 g, 4.47 mmol) was dissolved in DMF (10 mL) and the solution was cooled to 0° C. Sodium hydride (0.32 g of an oil dispersion, 8.04 mmol) was added, stirred for 30 min, and then 3-fluoropropyl bromide (1.13 g, 8.04 mmol) was added; this mixture was warmed to room temperature and stirred for 4 hr. A saturated aqueous solution of ammonium chloride (20 mL) was added and the mixture was extracted with ethyl acetate (4×50 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated to an oil which was dissolved in trifluoroacetic acid (20 mL) and stirred at room temperature for 18 hr. The mixture was evaporated to a residue which was purified by column chromatography (silica, gradient: 30% to 60% ethyl acetate/hexane) to give the desired product (1.0 g, 65%) as an oil.

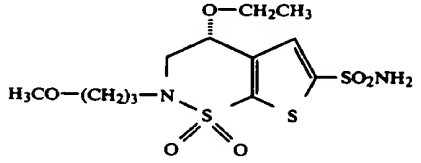
Step B:
4-Ethylamino-3,4-dihydro-2-(3-fluoropropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1 -dioxide hydrochloride

A solution of the product from Step A (0.99 g, 2.87 mmol) in THF (6.0 mL) at 0° C. was treated with p-toluenesulfonyl chloride (1.09 g, 5.75 mmol) and subsequently ethylamine (5 mL) in a manner identical to that described in Example 7, Step D to give the desired compound (700 mg, recrystallized from ethyl acetate/-methylene chloride): mp 238°–239° C. Analysis. Calculated for $C_{11}H_{19}ClFN_3O_4S_3$: C, 32.38; H, 4.69; N, 10.30. Found: C, 32.52; H, 4.90; N, 0.29.

Using modifications of the above procedure but substituting the appropriate alkyl halide in Step A and using either ethylamine or n-propylamine in Step B the following compounds were prepared:

1. 3,4-Dihydro-2-propyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 130°–133° C.;
2. 3,4-Dihydro-4-(2 -methylpropyl)amino-2-propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride hemihydrate, mp 145°–147° C.;
3. 3,4-Dihydro-2-(3-hydroxypropyl)-4-n-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 98°–100° C.;
4. 3,4-Dihydro-2-(3-hydroxypropyl)-4-(2-methylpropyl)amino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride hemihydrate, mp 110°–112° C.;
5. 3,4-Dihydro-2-(2-hydroxypropyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 194°–200° C.;
6. 3,4-Dihydro-2-(2-hydroxypropyl)-4-(2-methylpropyl)amino-2H-thieno[3.2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 181°–183° C.;
7. 3,4-Dihydro-2-(4-hydroxybutyl)-4-(2-methylpropyl)amino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 202° C.;
8. 4-Ethylamino-3,4-dihydro-2-(3-hydroxybutyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 73°–75° C.;
9. 4-Ethylamino-3,4-dihydro-2-(4-hydroxypentyl)-4-n-propylamino-2H -thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 187°–188° C.;
10. 3,4-Dihydro-2-(5-hydroxyhexyl)-4-(2-methylpropyl)amino-2H-thieno[3,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 187°–188° C.;
11. 4-Ethylamino-3,4-dihydro-2-(2,3,4,5-tetrahydrofuran-2-yl)methyl-4-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 142°–144° C.

EXAMPLE 10



-continued

R-(−)-4-Ethoxy-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Step A:

(R)-3,4-Dihydro-4-hydroxy-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

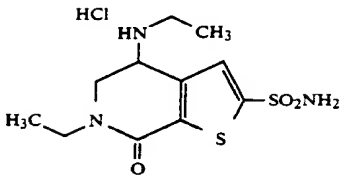
To a solution of (−)-β-chlorodiisopinocampheylborane (20.4 g, 63.5 mmol) in THF (20 mL) at −20° C. was added a solution of the product from Example 1, Step H (4.5 g, 12.7 mmol) in THF (60 mL) at −20° C.; this mixture was stirred for 48 hr maintaining this temperature. Diethanolamine (6,6 g, 63.5 mmol) was added and the solution allowed to warm to room temperature. The solvent was evaporated and the residue suspended in water (50 mL). This mixture was extracted with ethyl acetate (5×50 mL), and the combined extracts were washed with brine (15 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by column chromatography (silica, gradient: 50% to 60% ethyl acetate/-hexane) to give a white solid (3.9 g, 85%); mp 109°–111° C. Analysis: Calculated for $C_{10}H_{16}N_2O_6S_3$: C, 33.69; H, 4.53; N, 7.86. Found: C, 33.74; H, 4.48; N, 7.85.

Step B:

R-(−)-4-Ethoxy-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

To a solution of the product from Part A (2.81 g, 7.9 mmol) in acetonitrile (10 mL) at room temperature was added dimethylformamide dimethyl acetal (1.16 mL, 8.6 mmol); this solution was stirred for 2 hr and evaporated to dryness. The crude product was purified by chromatography (silica, 50% ethyl acetate/hexane) to give the desired protected sulfonamide derivative. This compound (2.54 g, 5.6 mmol) was dissolved in DMF (15 mL), cooled to 0° C., and sodium hydride (0.33 9 of a 60% oil dispersion, 8.33 mmol) was added. After stirring for 30 min, ethyl iodide (1.3 g, 8.3 mmol) was added and stirring continued, but at room temperature, for 2 hr. A saturated aqueous solution of ammonium chloride (50 mL) was added and the mixture extracted with ethyl acetate (3×50 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated to a residue which was dissolved in ethanol (3 mL), acetic acid (6 mL) and hydrazine (1.4 mL) were added and the mixture was heated at 55° C. for 24 hr. After cooling to room temperature, saturated aqueous sodium bicarbonate (30 mL) was added and the mixture was extracted with ethyl acetate (4×50 mL) The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and evaporated to a residue which was purified by column chromatography (silica, gradient: 30% to 50% ethyl acetate/hexane) to give a syrup (500 mg). $[\alpha]_D$ −3.91° (c=0.67, CH_3OH). Analysis. Calculated for $C_{12}H_{20}N_2O_{63}$: C, 37.48; H, 5.24; N, 7.29. Found: C, 37.61; H, 5.25; N, 7.18.

EXAMPLE 11



6-Ethyl-4-ethylamino-4,5,6,7-tetrahydro-7-oxo-thieno[2,3-b]pyridine-2-sulfonamide hydrochloride

Step A: 6-Ethyl-4,5,6,7-tetrahydro-4-(trifluoroacetamino)-7-oxo-thieno[2,3-b]pyridine

After cooling a solution of 4,5,6,7-tetrahydro-4-(trifluoroacetamino)-7-oxo-thieno[2,3-b]pyridine (1.0 g, 3.8 mmol) in DMF (10 mL) to −20° C., sodium hydride (273 mg, 11.4 mmol of a 60% oil dispersion) was added followed by ethyl bromide (1.7 mL, 22.7 mmol). This mixture was allowed to warm to room temperature. Stirring continued at this temperature for an additional hour and then the mixture was poured into ice water (100 mL). This aqueous mixture was extracted with ethyl acetate (4×100 mL) and the combined extracts were washed with brine (2×50 mL), dried ($MgSO_4$), and concentrated to a crude oil which was purified by column chromatography (silica, 5% methanol/methylene chloride) to give a yellow solid (0.85 g, 77%): mp 136°–138° C.

Step B:
6-Ethyl-4-amino-4,5,6,7-tetrahydro-7-oxo-thieno[2,3-b]pyridine

To a solution of the product from Step A (4.5 g, 15.4 mmol) in 50% aqueous methanol (80 mL) was added potassium carbonate (3.2 g, 23 mmol) and the mixture stirred at room temperature for 5 hr. The methanol was evaporated and the remaining aqueous mixture was acidified (pH 3), extracted with ethyl acetate (100 mL), the pH was adjusted to 9 and again extracted with ethyl acetate (3×200 mL). The combined extracts were evaporated to an oil which was purified by column chromatography (silica, 5% methanol/methylene chloride) to give the desired product as a yellow oil (2.7 g, 70%).

Step C:
6-Ethyl-4-ethylamino-4,5,6,7-tetrahydro-7-oxo-thieno[2,3-b]pyridine

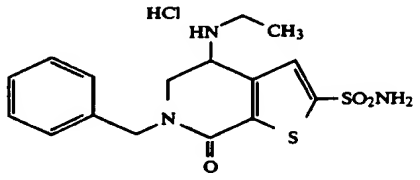
To a solution of the product from Step B (2.7 g, 13.8 mmol) in methanol (20 mL) at room temperature was added acetic acid (790 mL, 13.8 mmol) and sodium cyanoborohydride (867 mg, 13.8 mmol). After stirring this mixture for 18 hr concentrated HCl (1 mL) was added; when the evolution of gas ceased, the pH of the mixture was adjusted to 9 with 50% NaOH. The solvent was evaporated and the residue dissolved in ethyl acetate (200 mL); this solution was washed with brine (2×50 mL), dried ($MgSO_4$), and evaporated to an oil which was purified by column chromatography (silica, 5% methanol/methylene chloride) to give the desired product (1.85 g, 62%).

Step D:
6-Ethyl-4-ethylamino-4,5,6,7-tetrahydro-7-oxo-thieno[2,3-b]pyridine-2-sulfonamide hydrochloride

After cooling a solution of the product from Step C (1.7 g, 7.6 mmol) in THF (10 mL) to −78° C., a 1.7M

solution of t-butyllithium in pentane (13.4 mL, 22.8 mmol) was added and the reaction mixture stirred at −78° C. for 1 hr. Sulfur dioxide gas was passed through the reaction mixture until a pH of 3 was maintained. The mixture was allowed to warm to room temperature, and after stirring for 30 min was evaporated to a residue which was dissolved in water (100 mL). Sodium acetate (1.87 g, 22.8 mmol) and hydroxylamine-O-sulfonic acid (2.6 g, 22.8mmol) were added and the mixture stirred at room temperature for 18 hr and basified to pH 8. This aqueous mixture was extracted with ethyl acetate (3×200 mL) and the combined extracts were washed with saturated aqueous sodium bicarbonate (2×50 mL), dried ($MgSO_4$), and evaporated to an oil which was purified by column chromatography (silica, 5% methanol/methylene chloride) to give the free base as a foam (700 mg, 37%). This material was converted to the hydrochloride salt by treatment with ethanolic/-hydrogen chloride followed by recrystallization from methanol/methylene chloride (1:40) to give 600 mg of the desired product: mp 235° C. Analysis: Calculated for $C_{11}H_{18}ClN_3O_{S2}$: C, 38.88; H, 5.34; N, 12.30. Found: C, 38.98; H, 5.35; N, 12.26.

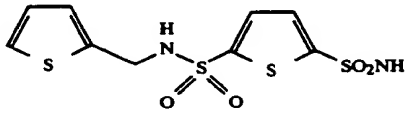
EXAMPLE 12



4-Ethylamino-4,5,6,7-tetrahydro-7-oxo-6-(phenylmethyl)-thieno[2,3-b]pyridine-2-sulfonamide hydrochloride

By following the same procedure as that described in Example 11, but substituting benzylchloride for ethyl bromide in Step A, the desired compound was obtained as a crystalline solid: mp 269–270C. Analysis: Calculated for $C_{16}H_{20}ClN_3O_3S_2$-H_2C, 45.67; H, 5.28; N, 10.00. Found: C, 45.65; H, 5.25; N, 10.11.

EXAMPLE 13



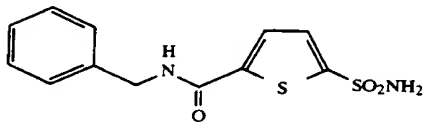
N-(2-Thienyl)methyl-2,5-thiophenedisulfonamide

To a solution of 5-sulfamoyl-thiophene-2-sulfonyl chloride (0.80 g, 3.1 mmol) in ethanol (10 mL) at 0° C. was added 2-thiophenemethylamine (0.67 mL, 6.51 mmol) and this mixture stirred at room temperature for 18 hr. After evaporation of solvent the residue was dissolved in ethyl acetate (200 mL) and this solution was washed with saturated aqueous sodium bicarbonate (2×50 mL), dried ($MgSO_4$), and evaporated to a crude material which was purified by column chromatography (silica, 5% methanol/methylene chloride) and recrystallization [methanol/methylene chloride (1:50)] to give the desired product (450 mg, 45%): mp 146°–148° C. Analysis: Calculated for $C_9H_{10}N_2O_4S_4$: C, 31.94; H, 2.98; N, 8.28. Found: C, 32.00; H, 2.96; N, 8.29.

By following the above procedure but using instead the appropriate arylalkylamine the following compounds were prepared:

1. N-(4-Trifluoromethylphenyl)methyl-2,5-thiophenedisulfonamide, mp 163°–164° C.;
2. N-(3,5-Dichlorophenyl)methyl-2,5-thiophenedisulfonamide, mp 141°–142° C.;
3. N-(3,4-Dichlorophenyl)methyl-2,5-thiophenedisulfonamide, mp 178°–179° C.;
4. N-(4-Methoxyphenyl)methyl-2,5-thiophenedisulfonamide, mp 149°–150° C.;
5. N-(4-Fluorophenyl)methyl-2,5-thiophenedisulfonamide, mp 166°–167° C.
6. N-[[4-(4-Morpholinyl methyl) phenyl]methyl]-2,5-thiophene disulfonamide, mp 161°–162° C.
7. N-[[3-(4-Morpholinylmethyl)phenyl]methyl]-2,5-thiophenedisulfonamide hydrochloride, mp 166°–168° C.

EXAMPLE 14



N-(Phenylmethyl)-5-(aminosulfonyl)-thiophene-2-carboxamide

To a mixture of benzylamine (0.91 mL, 8.5 mmol) and triethylamine (0.33 mL, 2.41 mmol) was added bis(triphenylphosphine)palladium(II) bromide (0.066 g, 0.08 mmol) and this mixture was stirred at 100° C. under an atmosphere of carbon monoxide for 19 hr. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (50 mL). The aqueous phase was washed with ethyl acetate (2×50 mL) and the combined organic phase was dried ($MgSO_4$) and concentrated. The solid was collected and washed with 50% ethyl acetate/hexane (40 mL) and hexane (30 mL). Concentration of the filtrate provided additional solid to give a total of 0.56 g (23 %) of crude product. Recrystallization from ethyl acetate/ethanol/hexane (1:1.5:1) gave the desired product: mp 203° C. Analysis: Calculated for $C_{12}H_{12}N_2O_3S_2$: C, 48:65; H, 4.05; N, 9.46. Found: C, 48.50; H, 4.11; N, 9.37.

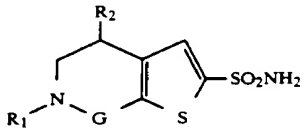
By following the above general procedure, the following compounds were prepared:

1. N-[(2-Thienyl)methyl)]-5-(amino-sulfonyl)-thiophene-2-carboxamide, mp 146°–148° C.
2. N-(methyl)-N-(phenylmethyl)-5-(amino-sulfonyl)-thiophene-2-carboxamide mp 173°–173.5° C.

Using the procedures described in equations 1 to 13, the Examples 1 to 14 and well known procedures, one skilled in the art can prepare the compounds disclosed herein and those listed in Tables 1 to 3.

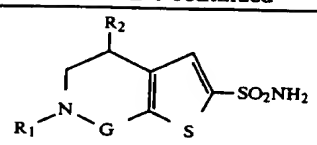
In the Tables the following symbols correspond to the chemical structures: Me is CH_3; Et is CH_2CH_3; n-Pr is $CH_2CH_2CH_3$; i-Pr is $CH(CH_3)_2$; i-Bu is $CH_2CH(CH_3)_2$; t-Bu is $C(CH_3)_3$ and Ph is C_6H_5.

TABLE 1



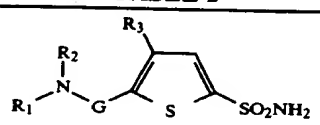
G	R_1	R_2
SO_2	CH_2CO_2-i-Pr	NH-n-Pr
SO_2	CH_2CO_2-i-Pr	NHEt
SO_2	$(CH_2)_3CO_2$-i-Pr	NHEt
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	H
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	OCH_2CH_2OH
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	OCH_2CH_2OMe
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	CH_2CH_3
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	CH_2OMe
SO_2	$(CH_2)_2N(CH_2CH_2)_2S$	NHEt
SO_2	$(CH_2)_2N(CH_2CH_2)_2SO_2$	OH
SO_2	CH_2CCH	NHEt
SO_2	$CH_2CCCH_2OCH_3$	NHEt
SO_2	$CH_2CONHMe$	NHEt
SO_2	$(CH_2)_2CONH(CH_2)_2OH$	NHEt
SO_2	C_6H_4—(3-OEt)	NHEt
SO_2	C_6H_4—(3-OH)	NHEt
SO_2	C_6H_4—(3-OH)	NH-n-Pr
SO_2	C_6H_4—(3-OMe)	NHEt
SO_2	C_6H_4—(4-OH)	NHEt
SO_2	C_6H_4—(4-OMe)	NHEt
SO_2	C_6H_4—(3-$OCHF_2$)	NHEt
SO_2	C_6H_4—(4-SO_2Me)	NHEt
SO_2	C_6H_4—(4-NHCOMe)	NHEt
SO_2	C_6H_4—(4-$CONMe_2$)	NHEt
SO_2	C_6H_3—(4-OH)—(3-CH_2NMe_2)	OEt
SO_2	C_6H_3—(4-OH)—(3-CH_2NMe_2)	H
SO_2	C_6H_3—(3,4-OH)	NHEt
SO_2	C_6H_3—(3,4-OMe)	NHEt
SO_2	C_6H_4—(4-$COCH_3$)	NHEt
SO_2	$CH_2C_6H_4$—(3,4-OMe)	NHEt
SO_2	$CH_2C_6H_3$—(4-OH)—(3-CH_2NMe_2)	OEt
SO_2	$CH_2C_6H_4$—(4-OMe)	NHEt
SO_2	$CH_2C_6H_4$—(3-OH)	NHEt
SO_2	CH_2[(2-CO_2Et)-pyridin-4-yl]	NHEt
SO_2	CH_2[(5-CO_2iPr)-thieno-2-yl]	NHEt
SO_2	$(CH_2)_3OH$	OH
SO_2	$(CH_2)_4OH$	OH
SO_2	$(CH_2)_5OH$	OH
SO_2	$(CH_2)_6OH$	OH
SO_2	$(CH_2)_4OH$	OEt
SO_2	$(CH_2)_4OH$	NH-n-Pr
SO_2	$(CH_2)_4OH$	NH-i-Bu
SO_2	$(CH_2)_3OCH_3$	OEt
SO_2	$(CH_2)_2OCH_3$	OEt
SO_2	CH_2-2-thienyl	OH
SO_2	CH_2—C_6H_5	OH
SO_2	$(CH_2)_2CH(OH)CH_3$	NHEt
SO_2	$(CH_2)_3CH(OH)CH_3$	NHEt
SO_2	$(CH_2)_2CH(OCH_3)CH_3$	NHEt
SO_2	$(CH_2)_3OH$	H
SO_2	$(CH_2)_3OCH_3$	H
SO_2	$(CH_2)_3OCOCH_3$	NHEt
SO_2	$(CH_2)_4OCOCH_3$	NHEt
SO_2	$(CH_2)_4CO_2Et$	NHEt
SO_2	$(CH_2)_3CO_2Et$	NHEt
SO_2	$(CH_2)_5CO_2Et$	NHEt
SO_2	$(CH_2)_4CO_2$-i-Pr	NHEt
SO_2	$(CH_2)_5CH_3$	NHEt
SO_2	$(CH_2)_4CH_3$	NHEt
SO_2	$(CH_2)_3CH(CH_3)_2$	NHEt
SO_2	CH_2-2-thiazole	OH
SO_2	CH_2-2-oxazole	OH
SO_2	CH_2-2-pyrimidine	OH
SO_2	CH_2-3-pyridazine	OH
SO_2	CH_2-2-pyrazine	OH
SO_2	CH_2-3-isothiazole	OH
SO_2	CH_2-3-isoxazole	OH
CO	$(CH_2)_3CO_2$-i-Pr	NHEt
CO	C_6H_4—(3-OH)	NHEt
CO	C_6H_4—(3-OH)	NH-n-Pr
CO	C_6H_4—(3-OMe)	NHEt
CO	C_6H_4—(4-OH)	NHEt
CO	C_6H_4—(4-OMe)	NHEt
CO	C_6H_4—(3-$OCHF_2$)	NHEt

TABLE 1-continued



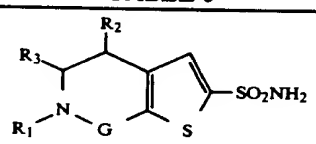
G	R_1	R_2
CO	C_6H_4—(4-SO_2Me)	NHEt
CO	C_6H_3—(4-OH)—(3-CH_2NMe_2)	OEt
CO	C_6H_3—(4-OH)—(3-CH_2NMe_2)	H
CO	C_6H_3—(3,4-OH)	NHEt
CO	C_6H_3—(3,4-OMe)	NHEt
CO	C_6H_4—(4-$COCH_3$)	NHEt
CO	$CH_2C_6H_4$—(3,4-OMe)	NHEt
CO	$CH_2C_6H_3$—(4-OH)—(3-CH_2NMe_2)	OEt
CO	$CH_2C_6H_4$—(4-OMe)	NHEt
CO	$CH_2C_6H_4$—(3-OH)	NHEt
CO	CH_2[(2-CO_2Et)-pyridin-4-yl]	NHEt
CO	CH_2[(5-CO_2iPr)-thieno-2-yl]	NHEt

TABLE 2



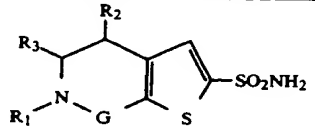
G	R_1	R_2	R_3
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	H	$COCH_3$
SO_2	$CH_2C_6H_4$—(3-OH)	CH_3	H
SO_2	$CH_2C_6H_4$—(3-OMe)	H	H
SO_2	$CH_2C_6H_4$—(4-OH)	H	CH_3
SO_2	$CH_2C_6H_4$—(4-OMe)	H	H
SO_2	$CH_2C_6H_4$—(4-OH)	H	CH_2OEt
SO_2	$CH_2C_6H_4$—(4-CONHMe)	H	CH_3
SO_2	$CH_2C_6H_4$—(4-SO_2NMe_2)	H	H
SO_2	$CH_2C_6H_4$—(3-SO_2Me)	H	CH_3
SO_2	$CH_2C_6H_4$—(4-$OCHF_2$)	CH_3	H
SO_2	$CH_2C_6H_3$—(4-OH)-3-(CH_2NMe_2)	CH_3	CH_3
SO_2	$CH_2C_6H_4$—(3-NHCOMe)	H	CH_3
SO_2	CH_2-4-pyridinyl	H	CH_3
SO_2	CH_2-2-pyridinyl	H	CH_3
SO_2	CH_2-2-thienyl	H	CH_3
SO_2	CH_2—(5-Me-2-thienyl)	H	H
CO	$(CH_2)_2N(CH_2CH_2)_2O$	H	$COCH_3$
CO	$CH_2C_6H_4$—(3-OH)	CH_3	H
CO	$CH_2C_6H_4$—(3-OMe)	H	H
CO	$CH_2C_6H_4$—(4-OH)	H	CH_3
CO	$CH_2C_6H_4$—(4-OMe)	H	H
CO	$CH_2C_6H_4$—(4-OH)	H	CH_3
CO	$CH_2C_6H_4$—(4-CONHMe)	H	CH_3
CO	$CH_2C_6H_4$—(4-SO_2NMe_2)	H	H
CO	$CH_2C_6H_4$—(3-SO_2Me)	H	CH_3
CO	$CH_2C_6H_4$—(4-$OCHF_2$)	CH_3	H
CO	$CH_2C_6H_3$—(4-OH)-3-(CH_2NMe_2)	CH_3	CH_3
CO	$CH_2C_6H_4$—(3-NHCOMe)	H	CH_3
CO	CH_2-4-pyridinyl	H	CH_3
CO	CH_2-2-pyridinyl	H	CH_3
CO	CH_2-2-thienyl	H	CH_3
CO	CH_2—(5-Me-2-thienyl)	H	H

TABLE 3



R_1	R_2	R_3
CH_3	H	$CH_2N(CH_2CH_2)_2O$
$(CH_2)_3OMe$	H	$CH_2N(CH_2CH_2)_2O$
$CH_2N(CH_2CH_2)_2O$	H	CH_2OH
$CH_2N(CH_2CH_2)_2O$	H	CH_2OMe
$CH_2N(CH_2CH_2)_2O$	H	CH_3

TABLE 3-continued



R_1	R_2	R_3
$(CH_2)_3OMe$	H	CH_2NHCH_3
$(CH_2)_3OMe$	H	$CH_2NH(CH_2)_2OMe$
$(CH_2)_4OMe$	NHEt	CH_3
C_6H_4—(4-OH)	NHEt	CH_3
C_6H_4—(3-OMe)	NHEt	CH_3
$CH_2C_6H_4$—(4-OH)	NHEt	CH_3

EXAMPLE 15

Ophthalmic Suspension

Ingredient	Concentration (wt %)
3,4-Dihydro-4-methoxy-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide (Compound)	3.0%
Hydroxypropylmethylcellulose	0.5%
Dibasic Sodium Phosphate	0.2%
Disodium Edetate	0.01%
Sodium Chloride	0.8%
Purified Water	q.s
Benzalkonium Chloride	0.01%
Polysorbate 80	0.1%
NaOH/HCl	pH 7.02

The Compound (0.09 g), benzalkonium chloride (0.03 g), polysorbate 80 (0.15 g) can be mixed together in water (1.23 g) and ball milled for approximately 4 h. A hydroxypropylmethylcellulose vehicle can be prepared by mixing 2% aqueous hydroxypropylmethylcellulose (40 g), sodium chloride (1.28 g), dibasic sodium phosphate (0.32 g), disodium edetate (0.016 g), sodium chloride (1.28 g) and water (35 g) together and the pH adjusted to 7.4 by the addition of 1N HCl (250 μL) . A portion of this vehicle (1.5 mL) can be added to the mixture containing the Compound to furnish the desired suspension.

EXAMPLE 16

Ophthalmic Solution

Ingredient	Concentration (wt %)
3,4-Dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride (Compound)	2.0%
Hydroxyethylcellulose	0.5%
Monobasic Sodium Phosphate	0.13%
Dibasic Sodium Phosphate	0.01%
Benzalkonium Chloride	0.01%
Disodium Edetate	0.01%
Purified Water	q.s.
NaCl (Osmolality = 282 mOsm)	0.4%
HCl/NaOH	pH 5.0

The Compound (0.06 g) and sodium chloride (0.014 g) were mixed together in water (1.44 g) and the pH of the solution was adjusted to 5.02 by the addition of 1N NaOH (10 μL). The hydroxyethylcellulose vehicle was prepared by mixing together monobasic sodium phosphate (0.26 g). dibasic sodium phosphate (0.02 g) and disodium edetate (0.02 g) in water (96.7 g). The benzalkonium chloride (2.0 g) and hydroxyethylcellulose were added to the mixture and the pH was adjusted to

5.01 by the addition of 1N HCl (100 μl) A portion of this vehicle (1.5 g) was added to the solution containing the compound and the pH was adjusted to 5.03 by the addition of 1N NaOH (10 μL).

EXAMPLE 17

Ophthalmic Gel

Ingredient	Concentration (wt %)
3,4-Dihydro-2-methyl-4-(2-methyl)propyl-amino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride (Compound)	1.0%
Mannitol	3.6%
Benzalkonium Chloride	0.01%
Carbopol	3.0%
HCl/NaOH	pH 5.0
Purified Water	q.s.

The mannitol (0.18 g), benzalkonium chloride (0.05 mL), Compound (0.1 g) and carbopol (0.15 g) can all be added to water (4.3 mL) and mixed well. The pH can be adjusted to pH 5.0 and purified water (q.s. to 5 mL) can be added and mixed well to form a gel.

EXAMPLE 18

Ophthalmic Solution

Ingredient	Concentration (wt %)
R-(+)-4-Ethylamino-3,4-dihydro-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfon-amide-1,1-dioxide hydrochloride (Compound)	2.27%
Hydroxypropylmethylcellulose	3.3%
Sodium Acetate Dihydrate	0.1%
Mannitol (Osmolality - 282 mOsm)	2.44%
Benzalkonium Chloride	0.01%
Disodium Edetate	0.01%
Purified Water	q.s.
HCl/NaOH	pH 5.0

The sodium acetate (0.2 g). disodium edta (0.02 g), benzylalkonium chloride (2.1 g of a 1% solution) and mannitol (5.32 g) were dissolved in water for injection (115 mL). The pH was adjusted to 5.0 with 1N sodium hydroxide and the final volume was adjusted to 117 mL with water for injection. Hydroxypropylmethylcellulose (83.0 g of an 8% solution) was mixed with the 117 mL of the acetate buffer solution to furnish the vehicle. To prepare the final formulation, 0.068 g of the Compound was diluted with vehicle to make 3.0 mL total volume and the pH was adjusted to 5.0 with 1N sodium hydroxide (5 μL).

EXAMPLE 19

Ophthalmic Solution

Ingredient	Concentration (wt %)
R-(+)4-Ethylamino-3,4-dihydro-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride (Compound)	1.69%
Hydroxypropylmethylcellulose	3.0%
Sodium Acetate trihydrate	0.1%
Mannitol (Osmolality = 317 mOsm)	2.4%
Benzalkonium Chloride	0.01%
Disodium Edetate	0.01%
Purified Water	q.s.

-continued

Ingredient	Concentration (wt %)
HCl/NaOH	pH 6.4

The above ingredients were mixed together in substantially the same manner as described in Example 18 to furnish the ophthalmic solution.

EXAMPLE 20

Ophthalmic Solution

Ingredient	Concentration (wt %)
R-(+)-3,4-Dihydro-2-(2-methoxy)ethyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride (Compound)	2.19%
Hydroxypropylmethylcellulose	3.0%
Sodium Acetate trihydrate	0.1%
Mannitol (Osmolality = 288 mOsm)	2.4%
Benzalkonium Chloride	0.01%
Disodium Edetate	0.01%
Purified Water	q.s.
HCl/NaOH	pH 5.0

The above ingredients were mixed together in substantially the same manner as described in Example 18 to furnish the ophthalmic solution.

EXAMPLE 21

Ophthalmic Suspension

Ingredient	Concentration (wt %)
(+)4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride (Compound)	2.0%
Hydroxypropylmethylcellulose	0.5%
Dibasic Sodium Phosphate	0.2%
Disodium Edetate	0.01%
Sodium Chloride	0.8%
Purified Water	q.s
Benzalkonium Chloride	0.01%
Polysorbate 80	0.1%
NaOH/HCl	pH 7.1

The above ingredients can be mixed together in substantially the same manner as described in Example 15 to furnish the ophthalmic suspension.

EXAMPLE 22

Ophthalmic Suspension

Ingredient	Concentration (wt %)
R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide (Compound)	2.0%
Hydroxypropylmethylcellulose	3.0%
Dibasic Sodium Phosphate	0.2%
Sodium Chloride	0.7%
Disodium EDTA	0.01%
Polysorbate 80	0.05
Benzalkonium Chloride Solution	0.01% + 5% xs
Sodium Hydroxide	q.s. pH = 7.2
Hydrochloric Acid	q.s. pH = 7.2
Water for Injection	q.s. 100%

The above ingredients were mixed together using a procedure similar to that described in Example 15 to furnish the ophthalmic suspension.

EXAMPLE 23

Ophthalmic Suspension

Ingredient	Concentration (wt %)
R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide (Compound)	2.0%
Hydroxypropylmethylcellulose	3.0%
Sodium acetate (trihydrate)	0.1%
Mannitol	4.1%
Disodium EDTA	0.01%
Benzalkonium Chloride Solution	0.01% + 5% xs
Sodium Hydroxide	q.s. pH = 5.0
Hydrochloric Acid	q.s. pH = 5.0
Water for Injection	q.s. 100%

The above ingredients were mixed together in a manner similar to the same general procedure described in Example 15 to furnish the ophthalmic suspension.

EXAMPLE 24

Ophthalmic Suspension

Ingredient	Concentration (wt %)
R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide (Compound)	2.0%
Carbomer 934P	0.5%
Sodium Chloride	0.4%
Mannitol	2.4%
Disodium EDTA	0.01%
Polysorbate 80	0.05%
Benzalkonium Chloride Solution	0.01% + 5% xs
Sodium Hydroxide	q.s. pH = 7.2
Hydrochloric Acid	q.s. pH = 7.2
Water for Injection	q.s. 100%

The above ingredients were mixed together using a method similar to the same general procedure described in Example 15 to furnish the ophthalmic suspension.

EXAMPLE 25

Ophthalmic Suspension

Ingredient	Concentration (wt %)
R-(+)-4-Ethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (Compound)	2.0%
Carbomer 934P	0.5%
Sodium Chloride	0.4%
Mannitol	2.4%
Disodium EDTA	0.01%
Polysorbate 80	0.05%
Benzalkonium Chloride Solution	0.01% + 5% xs
Sodium Hydroxide	q.s. pH = 7.2
Hydrochloric Acid	q.s. pH = 7.2
Water for Injection	q.s. 100%

The above ingredients can be mixed together using a method similar to the same general procedure described in Example 15 to furnish the ophthalmic suspension.

EXAMPLE 26

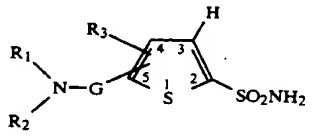
Ophthalmic Suspension

Ingredient	Concentration (wt %)
R-(+)-Ethylamino-3,4-dihydro-2-(4-methoxybutyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide (Compound)	2.0%
Carbomer 934P	0.5%
Sodium Chloride	0.4%
Mannitol	2.4%
Disodium EDTA	0.01%
Polysorbate 80	0.05%
Benzalkonium Chloride Solution	0.01% + 5% xs
Sodium Hydroxide	q.s. pH = 7.2
Hydrochloric Acid	q.s. pH = 7.2
Water for Injection	q.s. 100%

The above ingredients can be mixed together using a method similar to the same general procedure described in Example 15 to furnish the ophthalmic suspension.

We claim:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof wherein:

R^1 and R^3 are each saturated carbon atoms joined together to form a ring of 6 members in which said carbon atoms can be unsubstituted or substituted optionally with R_4;

R_2 is H; C_{1-8} alkyl; C_{2-8} alkyl substituted with OH, NR_5R_6, halogen, C_{1-4} alkoxy, C_{2-4}alkoxyC_{1-4}alkoxy, $OC(=O)R_7$, or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7}alkynyl unsubstituted or substituted optionally with C_1–C_3alkyl, C_1–C_3halo alkyl, OH, NR_5R_6, or C_{1-4}alkoxy; C_{1-3} alkyl substituted with phenyl or R_{10} either of which can be unsubstituted or substituted optionally with C_1–C_3alkyl, C_1–C_3halo alkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2; C_{2-4} alkoxy substituted optionally with NR_5R_6, halogen, C_{1-4} alkoxy, or $C(=O)R_7$; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2;

R_4 is OH; C_{1-4} alkyl unsubstituted or substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; NR_5R_6; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2;

R_5 & R_6 are the same or different and are H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6,

or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; $C_{1-2}alkylC_{3-5}cycloalkyl$; $C(=O)R_7$ or R_5 and R_6 can be joined to form a ring selected from the group consisting of pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine, and thiazolidine 1,1-dioxide, which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl, C_{1-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on nitrogen with C_{1-4} alkoxy, $C(=O)R_7$, $S(=O)_mR_8$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on sulfur by $(=O)_m$, wherein m is 0–2;

R_7 is C_{1-8} alkyl; substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_9$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen or C_{1-4} alkoxy; NR_5R_6; or phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, halogen, C_{1-3} alkyl, C_{1-3} haloalkoxy, $(CH_2)_nNR_5R_6$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein n is 0 or 1 and m is 0–2;

R_8 is C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$;

R_9 is C_{1-4} alkyl; C_{1-4} alkoxy; amino, C_{1-3} alkylamino, or di-C_{1-3} alkylamino;

R_{10} is a monocyclic ring system selected from the group consisting of furan, thiophene, pyrrole, pyrazole, imidazole, triazole, tetrazole, oxazole, isoxazole, isothiazole, thiazole, thiadiazole, pyridine, pyrimidine, pyridazine, and pyrazine; and

G is SO_2.

2. The compound of Claim 1 wherein: R_3 is in the 4-position and GNR_1R_2 is in the 5-position.

3. The compound of Claim 2 wherein:

R_2 is H; C_{1-8} alkyl; C_{2-8} alkyl substituted with OH, NR_5R_6, halogen, C_{1-4} alkoxy, $C_{2-4}alkoxyC_{1-4}alkoxy$, $OC(=O)R_7$, or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with C_1–C_3alkyl, C_1–C_3halo alkyl, OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-3} alkyl substituted with phenyl or R_{10} either of which can be unsubstituted or substituted optionally with C_1–C_3alkyl, C_1–C_3Halo alkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2; C_{2-4} alkoxy substituted optionally with NR_5R_6, halogen, C_{1-4} alkoxy, or $C(=O)R_7$; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2.

4. The compound of Claim 3 wherein:

R_2 is C_{1-8} alkyl; C_{2-8} alkyl substituted with OH, NR_5R_6, halogen, C_{1-2} alkoxy, $C_{2-4}alkoxyC_{1-4}alkoxy$, $OC(=O)R_7$, or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; phenyl, or R_{10}, unsubstituted or substituted optionally with C_1–C_3alkyl, C_1–C_3halo alkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2; C_{1-3} alkyl substituted with phenyl or R_{10} either of

which can be unsubstituted or substituted optionally with C_1–C_3alkyl, C_1–C_3halo alkyl OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2.

5. The compound of Claim 4 wherein:

R_4 is OH; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; or NR_5R_6; phenyl, or R_{10} unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2.

6. The compound of Claim 1 wherein:

R_4 is OH; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; or NR_5R_6; phenyl, or R_{10}, unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2.

7. A compound selected from the group consisting of:

R-(+)-4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno 1,2-thiazine-6-sulfonamide-1,1-dioxide;

(R)-4-Ethylamino-3,4-dihydro-2-(3-methoxyphenyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-4-Ethylamino-2-(4-hydroxy-phenyl)-3,4-dihydro-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-4-Ethylamino-3,4-dihydro-2-(3-hydroxy-phenyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-4-Ethylamino-3,4-dihydro-2-(4-hydroxy-phenylmethyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-4-Ethylamino-3,4-dihydro-2-(3-methoxy-phenylmethyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

R-(+)-4-Ethylamino-3,4-dihydro-2-(4-methoxybutyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

R-(+)-4-Ethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

R-(+)-4-Ethylamino-3,4-dihydro-2-(6-hydroxyhexyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-3,4-Dihydro-2-(3-hydroxypropyl)-4-(2-methylpropyl)amino-2H-thieno -1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-4-Ethylamino-3,4-dihydro-2-(3-hydroxy-phenylmethyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(3-methoxy-phenyl)-4-(2-methylpropyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(4-hydroxy-phenyl)-4-(2-methylpropyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(3-methoxy-phenyl)-4-propylamino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(3-hydroxy-phenyl)-4-propylamino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(3-hydroxy-phenyl)-4-(2-methyl-propyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(4-methoxybutyl)-4-(2-methyl-propyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(3-methoxypropyl)-4-(2-methyl-propyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-4-Cyclopropylmethylamino-3,4-dihydro-2-(2-propenyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-4-Cyclopropylmethylamino-3,4-dihydro-2-(4-methoxybutyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-4-Cyclopropylmethylamino-3,4-dihyro-2-(3-methoxypropyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-4-Cyclopropylmethylamino-3,4-dihydro-2-propyl-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(2-methylpropyl)-4-(2-methyl-propyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-4-Cyclopropylmethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-4-(2-methylpropyl)amino-2-propyl-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(4-hydroxybutyl)-4-(2-methyl-propyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-3,4-Dihydro-2-(4-hydroxybutyl)-4-propylamino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide.

8. A formulation for controlling intraocular pressure comprising a therapeutically effective amount of the compound of Claim **1** in a pharmaceutically acceptable carrier.

9. A formulation for controlling intraocular pressure comprising a therapeutically effective amount of the compound of Claim **7** in a pharmaceutically acceptable carrier.

10. The formulation of Claim **8** wherein the compound concentration is between 0.1 and 10% by weight.

11. The formulation of Claim **9** wherein the compound concentration is between 0.1 and 10% by weight.

12. The formulation of Claim **10** wherein the compound concentration is between 0.1 and 10% by weight.

13. A method for controlling intraocular pressure which comprises topically administering to the affected eye a therapeutically effective amount of the compound of Claim **1**.

14. A method for controlling intraocular pressure which comprises topically administering to the affected eye a therapeutically effective amount of the compound of Claim 7.

* * * * *

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Dean et al.

U.S. Serial Number: 08/019,011

Filed: February 18, 1993

Examiner: Ford, J.

Group Art Unit: 1202

For: SULFONAMIDES USEFUL AS CARBONIC ANHYDRASE INHIBITORS

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being telecopied to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, (703) 308-4556, on this date pursuant to the instructions of Della Collins.

June 20, 1994
Date

Diana L. Hunt
Name

Diana L. Hunt
Signature

TERMINAL DISCLAIMER AND FEE PURSUANT TO 35 CFR 1.32 (b) AND 1.20(d)

The Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

The Commissioner is authorized to deduct $110.00 from Deposit Account No. 01-0682. The Commissioner is authorized to deduct any underpayment to Deposit Account No. 01-0682. Two copies of this submission are enclosed.

Petitioner, Alcon Laboratories, Inc., a corporation of the State of Delaware, and having an office at Fort Worth, Texas, represents that it is the Assignee of the entire right, title, and interest in and to U.S. Application Serial No. 08/019,011, entitled Sulfonamides Useful as Carbonic Anhydrase Inhibitors, filed on February 23, 1994. An Assignment was recorded on February 28, 1994, on Reel 6879, Frame 076.

Petitioner further represents that it is the assignee of the entire right, title, and interest in and to United States Serial Number 618,765, now United States

Patent No. 5,153,192 issued October 6, 1992, by virtue of the Assignment, recorded on November 27, 1990, on Reel 5531, Frame 0559.

Petitioner hereby disclaims the terminal part of any patent granted on U.S. Application Serial No. 08/019,011 which would extend beyond the expiration date of U.S. Patent No. 5,153,192 which expires October 6, 2009.

Petitioner further agrees that any patent issuing on said U.S. Patent Application Serial No. 08/019,011 shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to said U.S. Patent No. 5,153,192, this agreement to run with any patent granted on said U.S. Patent Application Serial No. 08/019,011 and to be binding upon the grantee, its successors and assigns.

Petitioner, as assignee of U.S. Patent Serial No. 08/019,011 represents that to the best of assignee's knowledge and belief, title is in the assignee seeking to take action.

The undersigned Petitioner further declares that all statements made herein of its own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Respectfully submitted,

June 20, 1994
Date

Sally Yeager
Attorney of Record
for Alcon Laboratories, Inc.
Registration No. 32,757

Docket No. 1158C

CERTIFICATE UNDER 37 C.F.R. § 3.73(b)

Applicant: Thomas Robert Dean, Hwang Hsing Chen, and Jesse Albert May

Application No.: 08/019,011 **Filed:** February 18, 1993

For: Sulfonamides Useful as Carbonic Anhydrase Inhibitors

Alcon Laboratories, Inc., a Delaware corporation,
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application identified above. The assignment was recorded in the Patent and Trademark Office at Reel 6879, Frame 0076, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application identified above, to the current assignee as shown below:

1. From: _____ To: _____
   The document was recorded in the Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
   The document was recorded in the Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
   The document was recorded in the Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.

The undersigned has reviewed all the documents in the chain of title of the patent application identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date : June 23, 1994

Name : Sally S. Yeager

Title : Assistant General Counsel

Signature: Sally S. Yeager

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Dean et al.

U.S. Serial Number: 08/019,011

Filed: February 18, 1993

Examiner: Ford, J.

Group Art Unit: 1202

For: SULFONAMIDES USEFUL AS CARBONIC ANHYDRASE INHIBITORS

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on this date:

May 16, 1994
Date

Diana L. Hunt
Name

Diana L. Hunt
Signature

TERMINAL DISCLAIMER AND FEE PURSUANT TO 35 CFR 1.32 (b) AND 1.20(d)

The Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

The Commissioner is authorized to deduct $110.00 from Deposit Account No. 01-0682. The Commissioner is authorized to deduct any underpayment to Deposit Account No. 01-0682. Two copies of this submission are enclosed.

Petitioner, Alcon Laboratories, Inc., a corporation of the State of Delaware, and having an office at Fort Worth, Texas, represents that it is the Assignee of the entire right, title, and interest in and to U.S. Application Serial No. 08/019,011, entitled Sulfonamides Useful as Carbonic Anhydrase Inhibitors, filed on February 23, 1994. An Assignment was recorded on February 28, 1994, on Reel 6879, Frame 076.

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Patent No. 5,153,192 issued October 6, 1992, by virtue of the Assignment, recorded on November 27, 1990, on Reel 5531, Frame 0559.

Petitioner hereby disclaims the terminal part of any patent granted on U.S. Application Serial No. 08/019,011 which would extend beyond the expiration date of U.S. Patent No. 5,153,192 which expires October 6, 2009.

Petitioner further agrees that any patent issuing on said U.S. Patent Application Serial No. 08/019,011 shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to said U.S. Patent No. 5,153,192, this agreement to run with any patent granted on said U.S. Patent Application Serial No. 08/019,011 and to be binding upon the grantee, its successors and assigns.

Petitioner, as assignee of U.S. Patent Serial No. 08/019,011 represents that to the best of assignee's knowledge and belief, title is in the assignee seeking to take action.

The undersigned Petitioner further declares that all statements made herein of its own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Respectfully submitted,

May 14, 1996
Date

Sally Yeager
Registration No. 32,757
Attorney of Record

Docket No. 1158C

Instructions to Docket Clerk

COPY

The following papers have been filed: Terminal Disclaimer and Fee Pursuant to 35 CFR 1.32(b) and 1.20(d) (Duplicate); and Return Card

Description of paper: SULFONAMIDES USEFUL AS CARBONIC ANHYDRASE INHIBITORS

Name of Applicant: Dean, et al.

US Patent No. 5,378,703

Serial No.: ~~xxxxxxx~~

Atty. File No.: 1158C **Sender's Initials:** SSY:ss

Title (New Cases):

Date of filing paper May 28, 1998

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

920
911

In re: Dean et al.

EXPRESS MAILING LABEL No. EH623959239US

U.S. Patent No: 5,378,703

Issued: January 3, 1995

Examiner: Ford, J.

Group Art Unit: 1202

For: SULFONAMIDES USEFUL AS CARBONIC ANHYDRASE INHIBITORS

TERMINAL DISCLAIMER AND FEE PURSUANT TO 35 CFR 1.32 (b) AND 1.20(d)

The Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

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Petitioner, Alcon Laboratories, Inc., a corporation of the State of Delaware, and having an office at Fort Worth, Texas, represents that it is the Assignee of the entire right, title, and interest in and to U.S. Application Serial No. 08/019,011, now U.S. Patent No. 5,378,703 entitled Sulfonamides Useful as Carbonic Anhydrase Inhibitors, filed on February 18, 1994. An Assignment was recorded on February 28, 1994, on Reel 6879, Frame 076-079.

Petitioner further represents that it is the assignee of the entire right, title, and interest in and to United States Serial Number 775,313, now United States Patent No. 5,240,923 issued August 31, 1993, by virtue of the Assignment, recorded on

October 9, 1991, on Reel 5884, Frame 0338-0344.

Petitioner hereby disclaims the terminal part of any patent granted on U.S. Application Serial No. 08/019,011 which would extend beyond the expiration date of U.S. Patent No. 5,240,923 which expires August 31, 2010.

Petitioner further agrees that the patent issued on said U.S. Patent Application Serial No. 08/019,011 shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to said U.S. Patent No. 5,240,923, this agreement to run with the patent granted on said U.S. Patent Application Serial No. 08/019,011 and to be binding upon the grantee, its successors and assigns.

Petitioner, as assignee of U.S. Patent Serial No. 08/019,011 (5,378,703) represents that to the best of assignee's knowledge and belief, title is in the assignee seeking to take action.

The undersigned Petitioner further declares that all statements made herein of its own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Respectfully submitted,

May 28, 1998
Date

Sally Yeager
Attorney of Record
for Alcon Laboratories, Inc.
Registration No. 32,757

Docket No. 1158C

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Dean et al.

EXPRESS MAILING
LABEL No. EH623959239US

U.S. Patent No: 5,378,703

Issued: January 3, 1995

Examiner: Ford, J.

Group Art Unit: 1202

For: SULFONAMIDES USEFUL AS CARBONIC ANHYDRASE INHIBITORS

TERMINAL DISCLAIMER AND FEE PURSUANT TO 35 CFR 1.32 (b) AND 1.20(d)

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Patents and Trademarks
Washington, D.C. 20231

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October 9, 1991, on Reel 5884, Frame 0338-0344.

Petitioner hereby disclaims the terminal part of any patent granted on U.S. Application Serial No. 08/019,011 which would extend beyond the expiration date of U.S. Patent No. 5,240,923 which expires August 31, 2010.

Petitioner further agrees that the patent issued on said U.S. Patent Application Serial No. 08/019,011 shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to said U.S. Patent No. 5,240,923, this agreement to run with the patent granted on said U.S. Patent Application Serial No. 08/019,011 and to be binding upon the grantee, its successors and assigns.

Petitioner, as assignee of U.S. Patent Serial No. 08/019,011 (5,378,703) represents that to the best of assignee's knowledge and belief, title is in the assignee seeking to take action.

The undersigned Petitioner further declares that all statements made herein of its own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Respectfully submitted,

May 28, 1998
Date

Sally Yeager
Attorney of Record
for Alcon Laboratories, Inc.
Registration No. 32,757

Docket No. 1158C

APPENDIX F

Maintenance Fee Statements

FORM PTO-1536
REV. (4-89)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

MAINTENANCE FEE TRANSMITTAL FORM

Address to:
Commissioner of Patents and Trademarks
Box M. Fee
Washington, D.C. 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to "Commissioner of Patents and Trademarks, Box M. Fee, Washington, D.C. 20231" on May 5, 1998.

Name of person signing Diana L. Hunt
Signature Diana L. Hunt

Enclosed herewith is the payment of the maintenance fee(s) for the listed patent(s).

1. ☐ A check for the amount of $_____ for the full payment of the maintenance fee(s) and any necessary surcharge on the following patents is enclosed.
2. ☒ The Commissioner is hereby authorized to charge $1,050.00 to cover the payment of the fee(s) indicated below to Deposit Account No. 01-0682 .
3. ☒ The Commissioner is hereby authorized to charge any deficiency in the payment of the required fee(s) or credit any overpayment to Deposit Account No. 01-0682 .

Information required by 37 CFR 1.366(c)(columns 1 & 5). *Information requested under 37 CFR 1.366(d) (columns 2-4 & 6-9).*

	Patent Number* 1	Fee Code 2	Maintenance Fee Amount 3	Surcharge Amount 4	U.S. Serial Number* 5 [06/555/555]	Patent Date 6 mm/dd/yy	Application Filing Date 7 mm/dd/yy	Payment Year	Small Entity? 9
1	5,378,703	183	1,050.00	-	08/019,011	1/3/95	2/18/93	4	No
2									
3									
4									
5									
6									
7									
8									
	Sub-totals—Columns 3 & 4		1,050.00	-					
	Total Payment		1,050.00						

Use additional sheets for listing patents.

(For Office Accounting Use Only)

*Respectfully submitted:

PAYOR'S NUMBER (if assigned) 004691

Alcon Laboratories, Inc., Sally Yeager
(Payor's name) Reg. No. 32,757

(Payor's signature)

(817) 551-4031
(Payor's telephone number)

FEE ADDRESS Alcon Laboratories, Inc.
Patent Department, Q-148
6201 South Freeway
Fort Worth, Texas 76134-2099

Note: All correspondence will be forwarded to the "Fee Address" or the "Correspondence Address" if no Fee Address has been provided. 37 CFR 1.363

***WHERE MAINTENANCE FEE PAYMENTS ARE TO BE MADE BY AUTHORIZATION TO CHARGE A DEPOSIT ACCOUNT, FORM PTO-1536 SHOULD REFLECT BOTH THE PAYOR'S NAME AND SIGNATURE IN THE BOTTOM LEFT CORNER THEREOF.**

Instructions to Docket Clerk

The following papers have been filed: Maintenance Fee Transmittal Form (Duplicate) and Return Card

PATENT & TRADEMARK OFFICE
MAY 11 98
PATENT MAINTENANCE DIVISION

Description of paper:

Name of Applicant: Dean, et al.

Patent Serial No.: 5,378,703

Atty. File No.: 11538C **Sender's Initials:** SSY.dn

Title (New Cases):

May 5, 1998